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VOL. 30 OCTOBER, 1952 NUMBER 10

THE PREPARATION OF SOME STEROIDS CONTAINING DEUTERIUM[1]

BY B. NOLIN[2] AND R. NORMAN JONES

ABSTRACT

The preparation of several deuterated steroids is described, viz.,

(i) the trideuteroacetates of the following alcohols: $\Delta^{5,7,9}$-estratrienol-17β; $\Delta^{1,3,5:10}$-estratrienol-3-one-17 (*estrone*); androstanol-3α; androstanol-3β; androstanol-17β; pregnanol-20α; Δ^{5}-pregnenol-3β-one-20; Δ^{5}-pregnenol-3β-one-20-d_4-17,21; Δ^{5}-cholestenol-3β; $\Delta^{6,8}$-cholestadienol-3β; ergostanol-3β; Δ^{14}-ergostenol-3β; Δ^{22}-5-isoergostenol-3α.

(ii) Δ^{5}-pregnenol-3β-one-20-d_3-21 acetate; Δ^{5}-pregnenol-3β-one-20-d_4-17,21.

(iii) androstanone-3-d_4-2,4; cholestanone-3-d_4-2,4; $\Delta^{8:14}$-ergostenone-3-d_4-2,4; cholestanone-7-d_2-6; androstanone-17-d_2-16.

From difficulties encountered in the preparation of cholestanone-7-d_2-6, it is inferred that 7-ketones enolize less readily than 3-,17-, or 20-ketones.

INTRODUCTION

Although a number of steroids containing deuterium have been described in the literature, previous investigators have sought mainly to introduce deuterium atoms into tightly bound positions, to serve as labels in studies of steroid metabolism. The methods most commonly employed have involved the exchange of steroids with deuterium oxide and acetic acid in the presence of platinum catalysts (1, 2, 4), or the catalyzed addition of deuterium to unsaturated steroids (10, 12, 13). Recently, introduction of deuterium has also been effected by treatment of steroid bromides or mercaptols with "deuterized" Raney nickel (5).

This paper is concerned with the preparation of several steroids in which deuterium atoms are introduced at relatively labile positions, viz.,

(i) as CD_3 groups in the acetoxy radicals of steroid alcohols acetylated with acetic anhydride-d_6.

(ii) at C_{17} and C_{21} in the side chain of Δ^{5}-pregnenol-3β-one-20 (Δ^{5}-*pregnenolone*).

(iii) as CD_2 groups adjacent to the carbonyl groups of 3-, 7-, and 17-ketosteroids.

These compounds have been prepared for the study of their infrared absorption spectra (8), and a comparison of the positions of the infrared absorption bands in the normal and deuterized steroids has aided in the assignment of the bands

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[2] *National Research Council Postdoctorate Fellow*

between 1350 and 1500 cm.$^{-1}$ to the vibrations of specific methyl and methylene groups in the steroid molecule (7).

I. *Steroid Acetates*

Acetic anhydride-d_6 was synthesized from acetyl-d_3 chloride (3) and sodium acetate-d_3, both the acid chloride and the sodium salt themselves being prepared from acetic-d_3 acid (3, 6).

Thirteen steroid alcohols were acetylated with heavy acetic anhydride (Table I). In an initial investigation cyclohexyl acetate-d_3 was also prepared by direct esterification with acetic-d_3 acid in acidic solution.

II. *Steroids Containing the $-CO-CD_3$ Side Chain*

The method employed for the introduction of the CD_3 group into the side chain of Δ^5-pregnenolone was similar to that used by MacPhillamy and Scholz (11) for the preparation of 21-C^{14}-progesterone. Δ^5-3β-acetoxyetiocholenic acid chloride (I) was treated with dimethylcadmium-d_6 to yield Δ^5-pregnenolone-d_3-21 acetate (II). The organocadmium compound was prepared *in situ* from the Grignard derivative of methyl-d_3 bromide.

When Δ^5-pregnenolone-d_3-21 acetate was hydrolyzed in the normal manner with sodium hydroxide in aqueous ethanol, the product isolated contained no excess deuterium and the infrared absorption spectrum was identical with that of normal Δ^5-pregnenolone (VII). It was therefore evident that the deuterium atoms in the C_{21}-d_3 group were lost during the hydrolysis of the acetate group, presumably as a result of enolization of the 20-ketone in alkaline solution.

The deuterated C_{21} methyl group was protected by carrying out the hydrolysis of the acetate with sodium carbonate in deuterium oxide and methanol-*d*. By this procedure some deuterium was introduced at C_{17} and some also into the hydroxyl group (III); the latter was readily displaced by exchange with methanol in neutral solution to yield Δ^5-pregnenolone-d_4-17,21 (IV). Both the light and heavy acetates of (IV) were also prepared (V, VI).

Since enolization of the 20-keto group occurred during the alkaline hydrolysis of the acetate group, there existed a possibility that the product might contain appreciable quantities of Δ^5-17-iso-pregnenolone-d_4-17,21. This was largely ruled out by the fact that a sample of normal Δ^5-pregnenolone prepared from I by the same procedure gave the correct optical rotation. The molecular rotations of Δ^5-pregnenolone and Δ^5-17-isopregnenolone are $+89°$ and $-433°$ respectively (in acetone solution) so that quite small traces of the 17-stereoisomer would have been detected by this means.

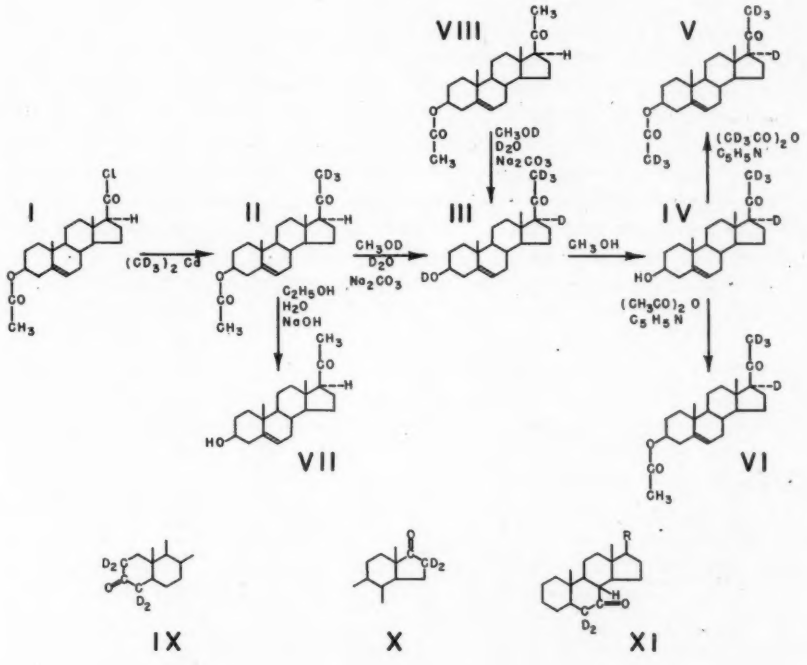
Δ^5-Pregnenolone-d_4-17,21 was also prepared directly by hydrolysis of Δ^5-pregnenolone acetate (VIII) with sodium carbonate in deuterium oxide and methanol-*d*. The resultant deuterated Δ^5-pregnenolone, after treatment with methanol and purification, gave an infrared spectrum identical with that of (IV), and contained 3.4 atoms of deuterium per molecule.

III. *Ketosteroids Deuterated in the α-Methylene Groups*

The 3-ketosteroids listed in Table II, on treatment with sodium carbonate in deuterium oxide and methanol-*d*, underwent deuterium exchange to the extent

of 3.7–3.8 atoms of deuterium per molecule, from which it is inferred that the methylene at both C_2 and C_4 participate in the enolization to yield IX as the principal product. Under the same conditions androstanone-17 exchanged to the extent of 2.12 atoms of deuterium per molecule. Since the 17-ketone can enolize in one way only, the product must be principally the C_{16}-d_2 derivative (X).

When cholestanone-7 was treated in a similar manner to the 3-, 17-, and 20-ketosteroids, the product contained only 0.59 atom of deuterium per molecule, and even under more forcing conditions of enolization, using sodium deuteroxide instead of sodium carbonate, the deuterium content could not be increased above 1.81 atoms per molecule.



Since 7-ketosteroids contain three potentially enolizable hydrogen atoms, two at C_6 and one at C_8, the structure of this product is in doubt. It is assumed tentatively that the major component has the C_6-d_2 structure (XI), but some material containing deuterium at C_8 may also be present. The infrared absorption spectrum does not serve to differentiate these; the disappearance of an absorption band at 1433 cm.$^{-1}$ which is observed to occur on deuteration of cholestanone-7 (8) requires only that *one* of the hydrogen atoms at C_6 be exchanged.

EXPERIMENTAL*

I. *Steroid Acetates*

Acetic Anhydride-d_6

Acetic-d_3 acid, prepared by the decarboxylation of malonic acid exchanged with deuterium oxide, was neutralized with aqueous sodium carbonate solution. The solution was evaporated to dryness and the resultant trihydrate decomposed by heating at 160° C. under vacuum. One equivalent of acetyl-d_3 chloride was added dropwise on to the dry salt and the anhydride distilled off. B.p. 137.0–138.2° C.; n_D^{20} 1.3881.

Cyclohexyl Acetate-d_3

A mixture of freshly distilled cyclohexanol (2.0 ml.), acetic-d_3 acid (2.5 ml.), and concentrated sulphuric acid (0.13 ml.) was refluxed for one hour. The cooled reaction mixture was diluted with water and extracted with ether. The ethereal solution was washed with aqueous sodium hydroxide, water, and dried with anhydrous sodium sulphate. After removal of the ether the residue was fractionally distilled under reduced pressure. B.p. 174.2–174.8° C.; n_D^{20} 1.4413.

Steroid Trideuteroacetates

The steroid alcohols (10–20 mgm.) were dissolved in dry pyridine (0.2 ml.), an equal volume of acetic anhydride-d_6 was added, and the mixture allowed to stand at room temperature overnight. The excess acetic anhydride-d_6 and pyridine were removed by vacuum distillation, and the residual trideuteroacetate purified by crystallization or high vacuum sublimation. The physical constants of the trideuteroacetates prepared in this manner are listed in Table I.

TABLE I

STEROID TRIDEUTEROACETATES

Steroid alcohol	M.p., °C.	
	Trideuteroacetate	Normal acetate
$\Delta^{5,7\ 9}$-Estratrienol-17β	98.0—101.0	—
Estrone	122.4—124.4	125.2—126.2
Androstanol-3α	133.6—134.6	133.2—134.0
Androstanol-3β	85.5— 86.4	85.0— 86.2
Androstanol-17β	75.5— 77.5	77.3— 79.3
Pregnanol-20α	127.3—127.8	—
Δ^5-Pregnenol-3β-one-20	141.3—142.5	142.5—144.7
Δ^5-Pregnenol-3β-one-20-d_4-17,21	140.2—141.9	142.5—144.7
Δ^5-Cholestenol-3β	112.7—114.4*	114.2—114.8
$\Delta^{6,8}$-Cholestadienol-3β	100.0—102.0	—
Ergostanol-3β	143.9—144.6	142.4—143.4
Δ^{14}-Ergostenol-3β	87.0— 88.0	90.0— 91.5
Δ^{22}-5-Isoergostenol-3α	108.9—110.2	106.6—109.4

* *Deuterium content 2.7 atoms per molecule.*

II. *Steroids Containing the $-CO-CD_3$ Side Chain*

Methyl-d_3 Bromide

Dry silver acetate-d_3 (31 gm.) was suspended in carbon tetrachloride (125 ml.)

* *All melting points are corrected.*

in a three-necked 0.5 liter flask provided with a dropping funnel, a gas inlet tube, and an efficient vertical water-cooled condenser. The upper end of the condenser led into two gas wash-bottles containing 40% potassium hydroxide solution, followed by two traps cooled in dry ice – acetone to receive the crude methyl-d_3 bromide.

The reaction mixture was cooled in iced water and stirred magnetically while bromine (13 ml.) was added dropwise at a rate sufficient to maintain a steady evolution of carbon dioxide without inducing an excessive temperature rise. After the bromine was added, the flask was warmed slowly and refluxed until the evolution of gas diminished. The mixture was then allowed to cool and a stream of nitrogen passed through the system for 30 min. The material collected in the traps was dried with Drierite and submitted to repeated fractional distillation. Some 2.4 ml. of deuterated methyl bromide were obtained after four distillations, corresponding to 25% of the theoretical yield.* The deuterium content, as determined by mass spectrometry, was 2.7 deuterium atoms per molecule.

Δ^5-Pregnenolone-d_3-21 Acetate (II)

The Grignard derivative of methyl-d_3 bromide was prepared from magnesium turnings (0.275 gm.) and methyl-d_3 bromide (0.65 ml.) in dry ether (20 ml.). Cadmium bromide (3.0 gm.) was added and the reaction mixture refluxed for two hours with magnetic stirring. A solution of Δ^5-3β-acetoxyetiocholenic acid chloride (I) (2.14 gm.) in benzene (20 ml.) was added dropwise, followed by 5 ml. of benzene. The reaction mixture was refluxed for two hours, and then cooled to room temperature. The product was decomposed with water (8 ml.) and 10% hydrochloric acid (12 ml.), stirred for 30 min., and allowed to stand overnight.

The product was extracted with ether and the ethereal solution, after washing successively with 5% sodium bisulphite, sodium hydroxide, and water, was dried with anhydrous sodium sulphate. On removal of the solvent there remained 1.25 gm. of crude Δ^5-pregnenolone-d_3-21 acetate (II). After two recrystallizations from methanol and a third from methanol–acetone–water the product melted at 138.2–140.2° C. and contained 2.67 deuterium atoms per molecule. The infrared absorption spectrum contained two maxima in the C = O stretching region at 1732 and 1702 cm.$^{-1}$ respectively in CCl_4 solution, indicative of the presence of the acetate and the 20-ketone group respectively (9).

The crude ester (0.77 gm.) was treated with 40 ml. of 0.1 *N* sodium hydroxide in 65% aqueous ethanol for 30 min. On working up the reaction product normal Δ^5-pregnenolone (VII) was isolated (m.p. 181.1–182.6° C.) with an infrared spectrum indistinguishable from that of the normal light compound, and exhibiting no deuterium enrichment.

Δ^5-Pregnenolone-d_4-17,21 (IV)

Crude Δ^5-pregnenolone-d_3-21 acetate (95 mgm.) was dissolved in a solution of anhydrous sodium carbonate (50 mgm.) in methanol-*d* (2.0 ml.) and deu-

* *The yields in this reaction were variable and in some preliminary runs with light silver acetate yields exceeding 50% were obtained. An improved method for the preparation of methyl-d_3 bromide from silver acetate-d_3 and bromine in a sealed vessel has subsequently been developed and will be described elsewhere.*

terium oxide (0.2 ml.). The solution was warmed on a water bath and a precipitate separated out. The precipitate was redissolved by the addition of 2.0 ml. of methanol-*d* and the solution refluxed for two hours. The alcohol was distilled off, the residue acidified with 5% aqueous hydrochloric acid, and the resultant suspension extracted with ether. The ether solution was washed with water, dried over anhydrous sodium sulphate, and the solvent removed. The product (III) assayed for 4.62 atoms of deuterium per molecule. It was treated several times with methanol and finally recrystallized from ether at −78° C. (m.p. 180.0–182.4° C.). The Δ^5-pregnenolone-d_4-17,21 (IV) so obtained assayed for 3.66 atoms of deuterium per molecule. The loss of 0.96 atom of deuterium per molecule on treatment of III with methanol in neutral solution was attributed to exchange of deuterium out of the hydroxyl group, and indicated the stability of the deuterium at C_{17} and C_{21} in neutral solution.

Δ^5-Pregnenolone-d_4-17,21 Acetate-d_3 (V)

This was prepared from (IV) by acetylation with acetic anhydride-d_6 as described above (Table I).

Δ^5-Pregnenolone-d_4-17,21 (IV) from Δ^5-Pregnenolone Acetate (VIII)

Δ^5-Pregnenolone acetate (6 mgm.) was dissolved in a solution of anhydrous sodium carbonate in methanol-*d* and deuterium oxide, the solution was refluxed overnight, and the product worked up as described above for (IV). The crude product was purified by high vacuum sublimation to yield 4.5 mgm. of material (m.p. 180.4–181.4° C.) which gave an infrared absorption spectrum identical with (IV) and contained 3.36 deuterium atoms per molecule.

Deuterium Content of Above Compounds

Since the deuterated methyl bromide, Δ^5-pregnenolone-d_3-21 acetate, and Δ^5-cholestenol-3β-acetate-d_3 all assayed for 2.7 atoms of deuterium per methyl group it seems probable that this corresponds to the deuterium content of the acetic acid used as starting material for all three preparations, and that no loss of deuterium by exchange occurred during the reactions described. This interpretation is supported by the fact that methane prepared from the same batch of acetic-d_3 acid by pyrolysis of the sodium salt with soda lime also assayed for 2.7 atoms of deuterium per molecule. Technical difficulties in sample preparation and dilution precluded an accurate evaluation of the deuterium content of the acetic-d_3 acid or acetic anhydride-d_6 by mass spectrometry.

III. *Ketosteroids Deuterated in the α-Methylene Group*

The ketosteroid (25 mgm.) was dissolved in methanol-*d* (4 ml.) and deuterium oxide (0.5 ml.), and 5 mgm. of anhydrous sodium carbonate were added. The reaction mixture was refluxed for 10 min., and evaporated to dryness. The residue was taken up in 4 ml. of methanol-*d* and 0.5 ml. of deuterium oxide, the solution was evaporated to dryness, refluxed, and the cycle repeated. The product was then extracted with anhydrous ether and the residue from the ethereal extract purified by high vacuum sublimation. The melting points and deuterium assays of the ketosteroids treated in this manner are listed in Table II.

In the case of cholestanone-7 it was necessary to replace the sodium carbonate by sodium deuteroxide to effect appreciable exchange.

TABLE II
DEUTERATED KETOSTEROIDS

Ketosteroid	M.p.,°C.	Deuterium atoms per molecule
Androstanone-3	98.7— 99.6	3.66
Cholestanone-3	129.1—129.5	3.69
$\Delta^{8:14}$-Ergostenone-3	122.5—125.5	3.80
Cholestanone-7	109.0—112.5	1.81
Androstanone-17	121.0—121.8	2.12

CONCLUDING REMARKS

Since the infrared absorption spectra of these compounds form the subject of a separate communication (8) they will not be discussed in detail here.

The suggestion from the ketone exchange reactions that the 7-ketone is less readily enolized then the 3-, 17-, or 20-ketosteroids might have useful implications in synthetic work. It also suggests that a study of the effects of hydrogen ion concentration, and other reaction conditions, on the rate and extent of deuterium exchange could provide rather precise information about the relative reactivities of carbonyl groups. Infrared spectrometry could be employed effectively to follow the progress of such exchange reactions, since enolizable methylene and methyl groups give rise to characteristic infrared absorption bands between 1350 and 1440 cm.$^{-1}$ (7). These bands all disappear on the introduction of a deuterium atom into the enolizable methylene group.

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STUDIES OF RDX AND RELATED COMPOUNDS

VII. RELATION BETWEEN RDX AND HMX PRODUCTION IN THE BACHMANN REACTION[1]

By S. Epstein and C. A. Winkler

ABSTRACT

The reactions to form RDX and HMX in Bachmann-type mixtures are comparable in respect of optimum nitric acid concentrations and in the fact that optimal amounts of acetic anhydride and ammonium nitrate are necessary for maximum yields of either explosive. The activation energies for formation of RDX and HMX were also found to be comparable, at 15 ± 1 kcal. per mole. However, withholding ammonium nitrate from the reaction mixture was found to have a more deleterious effect on RDX production than on HMX production. A mechanism is proposed which attempts in a general way to represent the relation between RDX and HMX production in the type of reaction mixtures used.

INTRODUCTION

An accurate method for analysis of HMX (cyclotetramethylenetetranitramine) in RDX (cyclotrimethylenetrinitramine), produced by the Bachmann reaction (1), was described in a preceding paper (2). In the present investigation the method was applied to a study of the relative rates of formation of RDX and HMX, and of the influence of certain factors on the relative yields of RDX and HMX in Bachmann type reaction mixtures.

EXPERIMENTAL

The materials employed were all of commercial grade. The hexamine, acetic acid, acetic anhydride, and ammonium nitrate were 99.0, 99.3, 95.0, and 99% pure respectively, while the nitric acid was 97% HNO_3.

Ammonium nitrate of accurately weighed amount was placed in 250 cc. Erlenmeyer flasks and the desired molar ratio of nitric acid added to bring the ammonium nitrate into solution. The ammonium nitrate was then reprecipitated as fine crystals by addition of acetic acid to the dilution required. Acetic anhydride of a designated amount was then added and the flask and its contents shaken in a constant temperature bath, the temperature of which was controlled within ± 0.2° C. After some minutes, the reaction was initiated by adding 5 cc. of 1 *M* hexamine – acetic acid solution, which caused any solid ammonium nitrate present to dissolve almost immediately.

By this sequence of addition and by using large proportions of acetic acid, any effect due to rate of solution of ammonium nitrate was practically eliminated and the total amounts of all reagents were brought together initially in a virtually homogeneous reaction medium. In this manner, satisfactory reproducibility of results was realized.

The reaction was stopped at the desired time by addition of approximately 30 cc. of water. Nitric acid (5 cc.) was then added and the resulting mixture simmered on a hot water bath for approximately four hours

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Contribution from the Physical Chemistry Laboratory, McGill University, Montreal, Que., with financial assistance from the National Research Council of Canada.

to destroy any BSX (1,7-diacetoxytetramethylene-2,4,6-trinitramine) present (1). Blank experiments with the product from reaction mixtures containing no ammonium nitrate showed that a three hour simmer was sufficient to destroy all the solids present. The flask was then filled to the neck with water and permitted to stand at room temperature for two days to ensure complete precipitation of RDX. The precipitate was filtered on a sintered glass crucible, dried at 105° C. for at least four hours, and weighed. Appropriate empirical corrections were applied for loss by solubility in the filtrate. The resulting RDX was analyzed for HMX by the method of differential homogeneous hydrolysis (2).

The percentage yield of RDX was calculated on the assumption that 100% yield represents the production of 2 moles RDX per mole hexamine. The HMX yield was calculated on the basis that 1 mole of hexamine is capable of yielding 1 mole of HMX. The reported yields generally represent the mean value for two or more identical experiments for which the results agreed within about 5%. The rates of production of RDX and HMX were estimated as initial rates, from tangents to the reaction-time curves at zero time.

RESULTS

Effect of Ammonium Nitrate on Relative Yields and Rates of Production of RDX and HMX

Results given in Fig. 1 show that, under the conditions of high dilution used

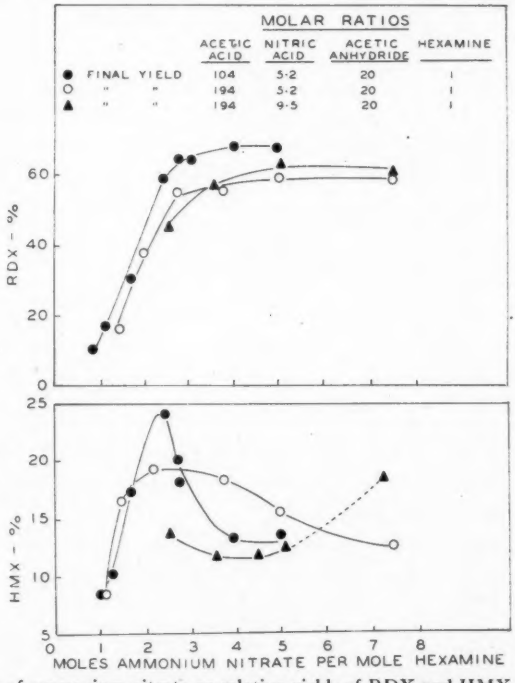


Fig. 1. Effect of ammonium nitrate on relative yields of RDX and HMX.

in these experiments, the optimal mole ratio of ammonium nitrate (about 2.75 moles per mole hexamine) for RDX production at 45° C. did not vary with dilution, but increased with increase of nitric acid concentration in the reaction mixture. One experiment at 55° C. showed no variation of the optimal ammonium nitrate mole ratio with temperature. The production of HMX showed rather remarkable sensitivity to the ammonium nitrate mole ratio and to dilution as shown in the lower curves of the figure; the optimum yield of HMX occurred at about 2.3 moles ammonium nitrate per mole hexamine.

The initial rates of RDX production increased until the optimal ammonium nitrate mole ratio was reached, but the initial rates of HMX production were practically independent of ammonium nitrate mole ratio in the range studied.

Effect of Nitric Acid on Relative Yields and Rates of Production of RDX and HMX

Optimum nitric acid – hexamine ratios were determined for the following conditions:

	Temp.				
	45°C.				55°C.
	Moles per mole hexamine				
Acetic acid	104	150	194	370	104
Acetic anhydride	20	40	20	20	20
Ammonium nitrate	3 and 2	3	3 and 6.25	3	3

The effect of dilution, temperature, and acetic anhydride on the optimum nitric acid mole ratio is shown in Fig. 2, while the effect of ammonium nitrate is shown in Fig. 3. For given conditions, the optimum nitric acid mole ratio for RDX production was usually about the same as that for HMX production. However, the optimum was much less pronounced for the latter, as a result of which the percentage HMX in the explosive produced generally showed a steady decline, which continued even after the optimum nitric acid mole ratio had been considerably exceeded.

Dilution with acetic acid at given ammonium nitrate mole ratio appeared to decrease the yield of RDX and to increase the HMX content of the explosive mixture (RDX + HMX). On the other hand, increase of ammonium nitrate mole ratio at given dilution increased the yield of RDX at the optimum nitric acid mole ratio, but decreased the HMX yield. Loss in RDX yield as a result of a limited increase in nitric acid beyond the optimum value, or by dilution at given ammonium nitrate level, was apparently reduced or overcome by increase in the ammonium nitrate mole ratio.

An increase of temperature increased the optimum nitric acid mole ratio for RDX production (from 5.2 to 6 moles per mole hexamine) without appreciable alteration in optimum yield. The optimum of about 5.2 moles of nitric acid per mole hexamine for HMX production at 45° C. gave way, however, to a steady increase in yield of HMX at 55° C. as the nitric acid level was increased from 4 to 8 moles per mole hexamine.

Doubling the acetic anhydride mole ratio (with adjustment of acetic acid

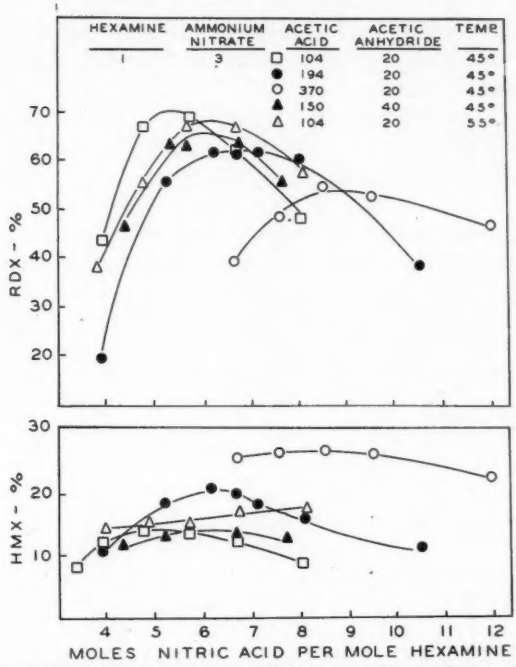


Fig. 2. Effect of dilution and acetic anhydride on optimum nitric acid mole ratio for RDX and HMX production.

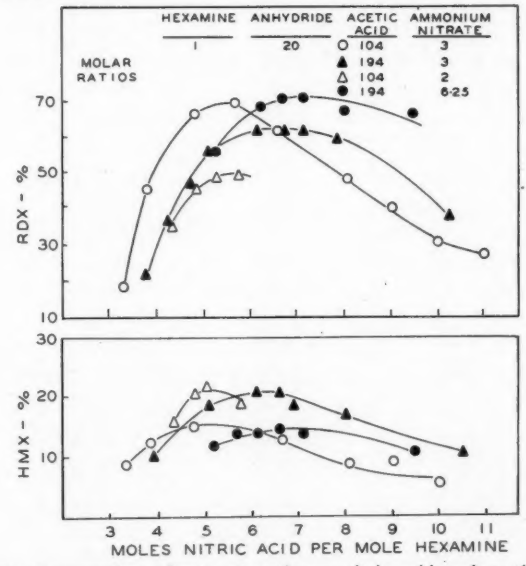


Fig. 3. Effect of ammonium nitrate on optimum nitric acid mole ratio for RDX and HMX production.

content to retain the same total volume) increased the optimum mole ratio of nitric acid somewhat and decreased the optimum HMX yield while the RDX yield was increased slightly.

The maximum rates of RDX and HMX formation were generally observed at the nitric acid mole ratios corresponding to optimum yields.

Effect of Acetic Anhydride on the Relative Yields and Rates of Formation of RDX and HMX

At given ammonium nitrate and nitric acid mole ratios (3 moles and 5.2 moles, respectively, per mole hexamine), the acetic anhydride content of the reaction mixture was changed over a range from 5 moles to 70 moles per mole hexamine, with corresponding adjustment of the acetic acid from 147 to 17 moles per mole hexamine to retain constant volume of the reaction mixture. The results, given in Fig. 4, show that in these systems of high dilution, there was little change in

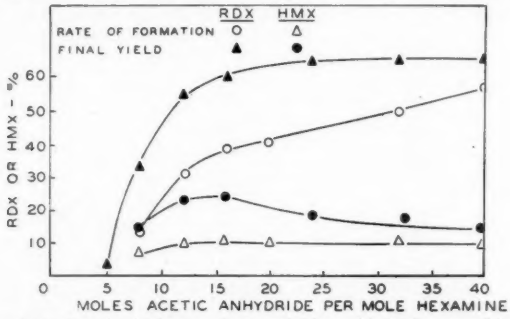


Fig. 4. Effect of acetic anhydride on relative yields and initial rates of formation of RDX and HMX.

yield of RDX, while the HMX yield fell off, beyond about 15 moles anhydride per mole hexamine. On the other hand, the initial rate of production of RDX continued to increase with anhydride mole ratio while the initial rate of HMX production reached a steady value.

Effect of Dilution on Rate of RDX and HMX Formation With and Without Adjustment to Optimum Nitric Acid Mole Ratio

The initial rates of formation of RDX and HMX were found to suffer somewhat less by dilution when the nitric acid mole ratio was adjusted to its optimal value than when no such adjustment was made. Some typical data were as follows:

	Volume of reaction medium (cc.) per 0.005 moles hexamine	Nitric acid – hexamine ratio	Initial rate, % yield per min.
RDX	104	5.2*	9.6
	194	5.2	1.25
	194	6.7*	2.0
HMX	104	5.2*	1.6
	194	5.2	0.36
	194	6.7*	0.5

**Optimal for dilution indicated.*

There is some indication from the relative extents to which dilution affected the rates that the reaction to form RDX is of higher order than that to produce HMX.

Effect of Temperature

The rates of production of RDX and HMX were determined at three temperatures (35°, 45°, and 55° C.), using reaction mixtures containing 0.075 moles (hexamine) per liter at each temperature. Initial rates were estimated independently by two individuals, using both large and small scale graphs, by drawing tangents at zero time. From the initial rates, an activation energy of 15 ± 1 kcal. per mole was estimated for both RDX and HMX formation.

Production of RDX and HMX when Addition of Ammonium Nitrate is Delayed

Studies of a type previously reported (4) were made to determine the effect of delayed addition of ammonium nitrate on the relative production of RDX and HMX under a variety of conditions. The only alteration in procedure was to add the ammonium nitrate at given intervals after reaction had been initiated in its absence by addition of hexamine. Reaction time was calculated from the time of addition of ammonium nitrate. The effect of increasing the length of time between initiation of reaction and addition of ammonium nitrate is shown in Fig. 5. As in the earlier study (4), serious loss (approximately 30%) of RDX was

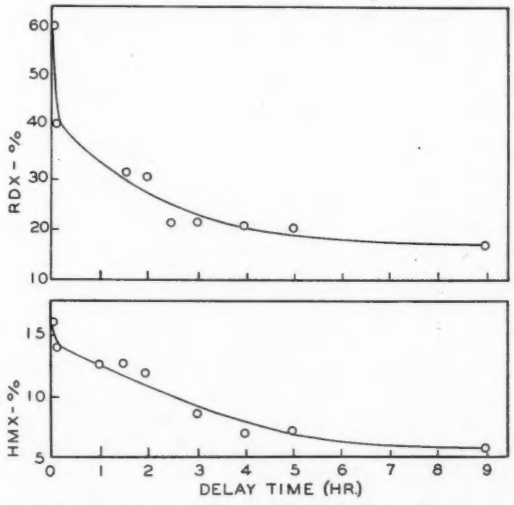


Fig. 5. Effect of delayed addition of ammonium nitrate on relative yields of RDX and HMX.

suffered when the addition of ammonium nitrate was delayed for as little as 15 min. The corresponding loss in HMX was not more than 10–12%.

Sufficiently prolonged delay (five hours or more) reduced the yield of both RDX and HMX to about one-third of the yield available when ammonium nitrate was added initially.

When the addition of ammonium nitrate was delayed 20 min. (i.e. beyond the

first rapid decrease in RDX yield), the relation between yield and mole ratio of ammonium nitrate eventually added was practically identical with that when the addition was not delayed. An optimal mole ratio for RDX production of 2.75 moles per mole hexamine, and for HMX production of 2.5 moles per mole hexamine, was observed. The maximum yields of RDX and HMX were 48% and 26% respectively. Excess ammonium nitrate decreased the HMX yield, but not the RDX yield, below this maximum value.

The optimum nitric acid mole ratio in systems where ammonium nitrate addition was delayed 20 min. was also identical with that when the addition was not delayed. Likewise, the activation energies for the formation of RDX and HMX, determined from initial rates, were essentially the same (15 and 13 kcal. respectively) when addition of ammonium was delayed 20 min. as when the nitrate was present from the start of reaction.

Comparison of the initial rates in reaction mixtures in which ammonium nitrate addition was delayed 20 min. with those obtained when the nitrate was not withheld revealed that the initial rate of HMX formation was essentially unaltered, while the initial rate of RDX production was reduced to about one-quarter the normal value by delaying the addition.

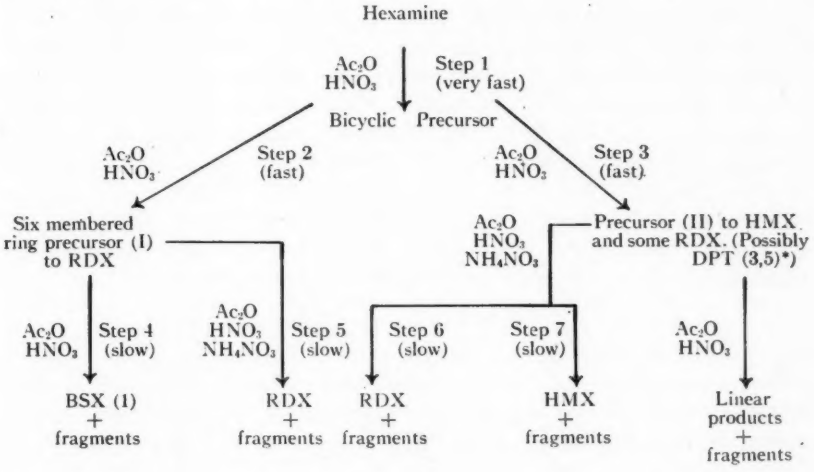
DISCUSSION

From the similarity in optimum nitric acid mole ratios and in changes of these mole ratios with varying conditions, together with the observation that optimum amounts of acetic anhydride and ammonium nitrate are necessary for maximum yields of both RDX and HMX, it seems reasonable to conclude that the reactions to produce RDX and HMX are not only similar, but closely related. It appears, however, that hexamine is converted into at least two compounds under the conditions of the experiments, from one of which both RDX and HMX may be derived, while the other gives rise only to RDX. This is indicated by the fact that when ammonium nitrate is withheld from the system, one-third of the prospective RDX is lost rapidly without correspondingly serious loss of HMX production, while longer delay in adding ammonium nitrate permits essentially parallel production of RDX and HMX. Also, with all other conditions constant, increasing amounts of ammonium nitrate or acetic anhydride increase markedly the rate of RDX, but not of HMX formation, while a decrease in HMX yield is roughly compensated by an increase in RDX yield. The rate-controlling step for the formation of HMX from the common precursor is therefore apparently not influenced by excesses of these reagents, while that for RDX formation is favorably affected.

Since at least one-half of the nitric acid necessary for maximum yield is required before any RDX or HMX is produced, whereas some RDX and HMX may be produced with as little as one-sixth of the amount of ammonium nitrate necessary for maximum yield, the hexamine molecule appears to be attacked first by nitric acid – acetic anhydride. Further indication of this sequence of reaction is obtained from the experiments in which the addition of ammonium nitrate is delayed. The initial rates of HMX formation in these experiments are of the same order of magnitude as those in the experiments in which ammonium

nitrate addition is not delayed. This might be expected if nitric acid and acetic anhydride determine the initial steps in the conversion of hexamine to the precursors forming HMX and RDX, and the subsequent addition of ammonium nitrate permits conversion of the precursors, which have not been destroyed, into RDX and HMX. Comparison of the slow rate at which nitric acid destroys the precursors common to HMX and two-thirds of the RDX with the much faster rate at which these precursors are converted to RDX and HMX on addition of ammonium nitrate indicates that ammonium nitrate does participate later in the formation of HMX and RDX, at least from their common precursor, and does not act merely as a buffer to prevent side reactions which might be favored over RDX formation in the absence of ammonium nitrate.

The majority of the results obtained in the present study would appear to be explained by the following general scheme:



followed by:

$$\text{Fragments} + Ac_2O + HNO_3 + NH_4NO_3 \rightarrow RDX + HMX$$

In this scheme, only the important general steps are included and it must be remembered that any one of the steps above may involve a series of chemical changes.

On the basis of the experimental evidence presented previously, steps 1, 2, and 3 are assumed to involve hexamine, nitric acid, and possibly acetic anhydride and acetic acid, but to be relatively little influenced by ammonium nitrate. If these steps are fast, the initial rates of formation of HMX in the experiments in which the addition of ammonium nitrate is delayed should be the same as those forming HMX when ammonium nitrate is present initially, since the

**1, 5–Endomethylene–3, 7–dinitrocyclo–2, 4, 6, 8–tetramethylene–1, 3, 5, 7–tetramine (dinitropentamethylenetetramine).*

concentration of precursor (II) should be the same regardless of whether ammonium nitrate was present initially or not.

Although one-third of the potential RDX is destroyed within a few minutes in the absence of ammonium nitrate, RDX and HMX may be produced from their common precursor after several hours. It would appear, therefore, that the reaction proceeds even in the absence of ammonium nitrate to the stage of the six-membered ring precursor and precursor (II). The six-membered ring precursor is converted to RDX in the presence of ammonium nitrate but is destroyed rapidly in its absence. However, precursor (II), common to HMX and part of RDX, is destroyed at a slower rate, with parallel destruction of both potential RDX and HMX. It may also be noted that in the absence of ammonium nitrate the destruction of potential RDX and HMX at 55° C. becomes very much slower after four hours. This may be due to destruction of most of precursor (II) after four hours, leaving only the relatively stable fragments to be converted to RDX and HMX. These considerations indicate that the steps 5, 6, and 7 are rate controlling in production of RDX in the Bachmann reaction.

If step 5 is eliminated by delayed addition of ammonium nitrate no decrease in the consumption of nitric acid should occur, since BSX (1) contains the same number of NO_2 groups as RDX and is formed in place of RDX. Also, although ammonium nitrate is necessary for the production of RDX through step 5, neither it nor its equivalent is incorporated in the RDX molecule, hence the consumption of ammonium nitrate should be the same with or without the occurrence of step 5. It is interesting to note that the optimal nitric acid and ammonium nitrate mole ratios are approximately the same whether step 5 is, or is not, present. It is also significant that the delayed addition of ammonium nitrate decreases the rate at which RDX is formed to one-third of that in the experiments where the addition of ammonium nitrate is not delayed. This is not surprising since it would be a remarkable coincidence if the rate of RDX formation through step 5 were the same as through 6. The elimination of step 5 should result in slow formation of RDX by conversion of precursor II and resynthesis of fragments.

The data presented for the effects of temperature, dilution, and varying proportions of reagents on the rates of formation and yields of RDX are in no way opposed to the mechanism suggested.

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STUDIES OF RDX AND RELATED COMPOUNDS

VIII. THERMOCHEMISTRY OF RDX REACTIONS[1]

By V. Gilpin and C. A. Winkler

ABSTRACT

The following heats of reaction have been determined, where the subscripts "*c*" and "*s*" refer to solid and solution respectively:

$Hexamine_{(c)} + HNO_{3\ (97.5\%)} = RDX_{(s)}$; $\Delta H = -88.0$ kcal. per mole.

$Hexamine\ mononitrate_{(c)} + HNO_{3(97.5\%)} = RDX_{(s)}$; $\Delta H = -69.2$ kcal. per mole.

$Hexamine\ dinitrate_{(c)} + HNO_{3(97.5\%)} = RDX_{(s)}$; $\Delta H = -41.7$ kcal. per mole.

$Hexamine_{(s)}$ + Bachmann reagents = $RDX_{(s)}$; $\Delta H = -140$ kcal. per mole.

$Hexamine\ mononitrate_{(s)}$ + Bachmann reagents = $RDX_{(s)}$; $\Delta H = -126$ kcal. per mole.

$Hexamine\ dinitrate_{(c)}$ + Bachmann reagents = $RDX_{(s)}$; $\Delta H = -118$ kcal. per mole.

These measurements, together with some on heats of solution of the reagents, indicate that hexamine dinitrate is an intermediate in the direct nitrolysis of hexamine to RDX, but that hexamine mononitrate is a probable intermediate in the Bachmann conversion of hexamine to RDX.

INTRODUCTION

While either hexamine or its mono- or di-nitrate salts may be used as starting materials for the preparation of RDX by the direct nitrolysis and Bachmann processes, it is a point of interest to determine whether the nitrate salts are in fact intermediates in the conversion of hexamine itself to RDX. The present thermochemical study of a number of associated reactions was made to obtain information about the part played by the nitrate salts in the nitrolysis of hexamine.

EXPERIMENTAL AND RESULTS

The calorimeter consisted simply of a 500 ml. widemouthed Dewar vessel, fitted with a cork stopper through which passed a thermometer, a mechanically driven stirrer, and a tube for introducing materials as desired. The bottom of the cork was soaked in paraffin and covered with aluminum foil to protect it against reaction fumes.

To measure ΔH, the temperature rise due to reaction was compared with the rise in temperature caused by the introduction of a known amount of heat into the liquor at the end of the reaction. The heat was introduced with a weighed Pyrex glass plummet held at 100° C. prior to transfer to the calorimeter. Temperature changes in the calorimeter were measured with a Beckmann thermometer. The method was tested by determining the heat of neutralization of sodium hydroxide with hydrochloric acid. Taking an average value for the specific heat of Pyrex between 20° C. and 100° C. from the expression (2)

$$c_t = 0.174 + 0.00036t\ (t = °C.),$$

corresponding to a water equivalent for the plummet of 3.73 gm., the heat of neutralization was found to be 13.7 kcal. at 24° C. Since this value is within 1%

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Contribution from the physical chemistry laboratory, McGill University, Montreal, Que., with financial assistance from the National Research Council.

of that generally accepted, the calorimeter was considered quite adequate for a study of RDX reactions, where reproducibility better than within a few per cent was not expected.

The Direct Nitrolysis Reaction

In all these experiments a large excess (100 ml.) of 97.5% nitric acid was used in the calorimeter to prevent uncontrollable fume-off. Weighed amounts of hexamine, hexamine mononitrate, or hexamine dinitrate were introduced into the calorimeter from a dry glass tube in which the solids had been brought to a temperature of 25.0° C. After observation of the rapid initial temperature rise by the Beckmann thermometer, the solution was again cooled to 25° C. by adding dry ice, whereupon the hot glass plummet was transferred to the calorimeter to obtain the heat capacity of the contents. Values of ΔH for nitrolysis of hexamine and its two nitrate salts are given in Table I. In the table, and in the discussion that follows, the subscripts "*c*" and "*s*" refer to solid and solution respectively.

The Bachmann Reaction

The reactants in these experiments were hexamine (or the appropriate nitrate), acetic anhydride, acetic acid, ammonium nitrate, and nitric acid. To quench the temperature rise and prevent the reaction becoming uncontrollable, glacial acetic acid was used as a diluent. A thermometer graduated in $\frac{1}{10}$° C. was used throughout, and all reactions were started at approximately 65° C.

Following a suggestion of Dr. L. Davy, Tennessee Eastman Co., a "dilute batch" was prepared from a large excess of acetic acid, plus a standard Bachmann batch without the hexamine. When the regular batch was added to this, allowing the temperature to rise from 65° C. to nearly 90° C., yields between 60% and 70% RDX were obtained.

Stock solutions were prepared as follows:

Hexamine (140 gm.) in acetic acid (230 gm.)—total volume 330 ml.; ammonium nitrate (250 gm.) in 97.5% nitric acid (312 gm.)—total volume 370 ml.; acetic anhydride 750 ml.

A hundredth part of each of these solutions constituted a batch. A mixture of acetic acid (60–80 ml.) and acetic anhydride (16–19 ml.) was heated to 75° C. and poured into the calorimeter. The temperature fell to about 65° C.; stirring was started, and continued while the rate of temperature change was established. The nitric acid – ammonium nitrate solution (7.4 ml.) was then introduced, causing the temperature to rise quickly to slightly above 65° C. Time–temperature readings were taken until the temperature had fallen to 65° C. when 0.01 moles of hexamine (3.3 ml. of the stock solution plus several milliliters of acetic acid) at 65° C. was poured into the stirred solution in the calorimeter. After the temperature had again reached a uniform rate of change, the plummet was transferred from a low temperature thermostat to the Bachmann liquor, and temperature changes followed as before. The water equivalent of the Pyrex plummet at the temperatures used was calculated to be 3.64 gm.

For experiments with hexamine mononitrate, the amount of nitric acid – ammonium nitrate solution used was reduced to 5.7 ml. to compensate for the

nitric acid added as the hexamine salt. The mononitrate was introduced into the calorimeter as an acetic acid solution at 65° C.

With hexamine dinitrate, the nitric acid – ammonium nitrate solution was further reduced to 3.8 ml. The dinitrate was introduced as a slurry in acetic acid, its temperature being 65° C.

The values of ΔH for the reactions studied under Bachmann conditions are given in Table I.

TABLE I
SUMMARY OF THERMAL DATA

Reaction	— ΔH(kcal./mole reactant)*	
	Direct nitrolysis	Bachmann
$Hexamine_{(c)} \rightarrow RDX_{(s)}$	88.0	146.5(calc.)
$Hexamine_{(s)} \rightarrow RDX_{(s)}$	83.2(calc.)	140
$Hexamine\ dinitrate_{(c)} \rightarrow RDX_{(s)}$	41.7	118
$Hexamine\ mononitrate_{(c)} \rightarrow RDX_{(s)}$	69.2	
$Hexamine\ mononitrate_{(s)} \rightarrow RDX_{(s)}$	74.6(calc.)	126
$Hexamine_{(c)} \rightarrow hexamine\ dinitrate_{(s)}$	33.5	
$Hex.\ mononitrate_{(s)} \rightarrow hex.\ dinitrate_{(s)}$	15.7	
$Hexamine_{(c)} + HAc \rightarrow hexamine_{(s)}$		6.5
$Hex.\ mononitrate_{(c)} + H_2O \rightarrow hex.\ mononitrate_{(s)}$	—5.4	

*Average of duplicate or triplicate experiments.
Values recorded here may be approximately 3% in error.

Additional Reactions

To permit calculations made later in this paper, certain auxiliary reactions were studied. The heat of formation of the dinitrate was determined using 65% nitric acid, with the same procedure as for the nitrolysis. For the conversion of mononitrate to dinitrate, a water solution of the mononitrate was introduced into 69% nitric acid. A blank using water alone was necessary to determine the heat of nitric acid dilution. The heat of solution of mononitrate in water was studied by the same methods as the nitrolysis reactions, and the heat of solution of hexamine by the methods used for the Bachmann reactions. Both heats of solution were determined at two different (very dilute) concentrations, and no significant variation of heat of dilution with concentration was noted. The values of ΔH for these various reactions are in Table I.

DISCUSSION

The production of RDX by direct nitrolysis of hexamine and hexamine dinitrate may be represented:

(1) $Hexamine_{(c)} + HNO_3\ (97.5\%) = RDX;\ \Delta H_1 = -88.0$ kcal.

(2) $Hexamine\ dinitrate_{(c)} + HNO_3\ (97.5\%) = RDX;\ \Delta H_2 = -41.7$ kcal.

If the nitrolysis of hexamine did not involve the dinitrate as an intermediate, (1) could be written:

(1*a*) $Hexamine_{(c)} + HNO_3\ (97.5\%) = hexamine_{(s)}$
(1*b*) $Hexamine_{(s)} + HNO_3\ (97.5\%) = RDX_{(s)}$ } $\Delta H_1 = -88.0$ kcal.

while if the dinitrate is formed in the process

(1*c*) Hexamine$_{(c)}$ + HNO_3 (97.5%) = hexamine$_{(s)}$
(1*d*) Hexamine$_{(s)}$ + HNO_3 (97.5%) = hexamine dinitrate$_{(s)}$
(1*e*) Hexamine dinitrate$_{(s)}$ + HNO_3 (97.5%) = $RDX_{(s)}$ } $\Delta H_1 = -88.0$ kcal.

Similarly (2) may be written:

(2*a*) Hexamine dinitrate$_{(c)}$ + HNO_3 (97.5%) = hexamine dinitrate$_{(s)}$
(2*b*) Hexamine dinitrate$_{(s)}$ + HNO_3 (97.5%) = $RDX_{(s)}$ } $\Delta H_2 = -41.7$ kcal.

Now, Delepine (1) found:

(3) Hexamine dinitrate$_{(c)}$ + aq = hexamine dinitrate$_{(s)}$; $\Delta H_3 = +14.3$ kcal.

Assuming the heat of solution of hexamine to be the same in water as in nitric acid (of all strengths) and subtracting (3) from (2*a* + 2*b*):

(4) Hexamine dinitrate$_{(s)}$ + HNO_3 (97.5%) = $RDX_{(s)}$; $\Delta H_4 = -56.0$ kcal.

But from the present study:

(5*a*) Hexamine$_{(c)}$ + HNO_3 (65%) = hexamine$_{(s)}$
(5*b*) Hexamine$_{(s)}$ + HNO_3 (65%) = hexamine dinitrate$_{(s)}$ } $\Delta H_5 = -33.5$ kcal.

Hence, adding (5*a* + 5*b*) to (4), a value is obtained for (1*c* + 1*d* + 1*e*) = -89.5 kcal.

This is in reasonably good agreement with the measured value of -88.0 kcal. for the nitrolysis of hexamine. Hence, it seems quite safe to conclude that the direct nitrolysis reaction with hexamine does go through the dinitrate stage.

Subtraction of (2) from (1) gives:

(6) Hexamine$_{(c)}$ + HNO_3 = hexamine dinitrate$_{(c)}$; $\Delta H_6 = -46.3$ kcal.

The thermochemical equations for the Bachmann type reactions studied will be written, with due consideration for the conditions employed:

(7) Hexamine$_{(s)}$ + Bachmann reagents = $RDX_{(s)}$; $\Delta H_7 = -140$ kcal.

(8) Hexamine dinitrate$_{(c)}$ + Bachmann reagents = $RDX_{(s)}$; $\Delta H_8 = -118$ kcal.

The solution of hexamine in glacial acetic acid corresponds to

(9) Hexamine$_{(c)}$ + acetic acid(glacial) = hexamine$_{(s)}$; $\Delta H_9 = -6.5$ kcal.*

whence

(10) Hexamine$_{(c)}$ + Bachmann reagents = $RDX_{(s)}$; $\Delta H_{10} = -146.5$ kcal.

Therefore, for the Bachmann reaction there is obtained from (10) − (8):

(11) Hexamine$_{(c)}$ + Bachmann reagents = hexamine dinitrate$_{(c)}$; $\Delta H_{11} = -28.5$ kcal.

Comparison of this with the previous value $\Delta H_6 = -46.3$ kcal. for the molar heat of conversion of hexamine to the dinitrate indicates that in the Bachmann reaction, part at least of the hexamine is not converted to the dinitrate. (No account is taken here of the different temperatures at which the direct nitrolysis and Bachmann reactions respectively were studied, but this should not introduce sufficient error to invalidate the comparison.)

The data obtained here point to the intermediate formation of the mononitrate in the Bachmann reaction with hexamine. If the mononitrate is an intermediate, then hexamine → hexamine mononitrate → RDX.

Now

(7) Hexamine$_{(s)}$ + Bachmann reagents = $RDX_{(s)}$; $\Delta H_7 = -140$ kcal.

and

**Delepine (1) found $\Delta H = -4.8$ kcal. for the solution of hexamine in water.*

(12) Hexamine mononitrate$_{(s)}$ + Bachmann reagents = RDX$_{(s)}$; ΔH_{12} = − 126 kcal.

From (7) and (12),

(13) Hexamine$_{(s)}$ + Bachmann reagents = hexamine mononitrate$_{(s)}$; ΔH_{13} = − 14 kcal.

It was not possible with the equipment used in these studies to measure satisfactorily the heat of conversion of hexamine to hexamine mononitrate. However, from data for the direct nitrolysis

(14) Hexamine mononitrate$_{(c)}$ + HNO_3 (97.5%) = RDX$_{(s)}$; ΔH_{14} = − 69.2 kcal.

(15) Hexamine mononitrate$_{(c)}$ + aq = hexamine mononitrate$_{(s)}$; ΔH_{15} = + 5.4 kcal.

whence

(16) Hexamine mononitrate$_{(s)}$ + HNO_3 (97.5%) = RDX$_{(s)}$; ΔH_{16} = − 74.6 kcal.

Taking $\Delta H_{(1a)}$ as −4.8 kcal., $\Delta H_{(1b)}$ may be calculated,

(1*b*) Hexamine$_{(s)}$ + HNO_3 (97.5%) = RDX$_{(s)}$; $\Delta H_{(1b)}$ = − 83.2 kcal.

From (16) and (1*b*)

(17) Hexamine$_{(s)}$ + HNO_3 (97.5%) = hexamine mononitrate$_{(s)}$; ΔH_{17} = − 8.6 kcal.

Previous calculations have shown that hexamine goes to RDX via the dinitrate in the direct nitrolyses reaction. A simple calculation indicates that the conversion of the mononitrate to RDX by direct nitrolysis probably goes through the dinitrate stage also. Hence, ΔH_{17} is to be compared with ΔH_{13}. The agreement between the two is not good, but it must be remembered that the estimation of these heats involves several much larger values, each of which may be in error by approximately ± 2 kcal. Although the agreement is not all that might be desired, it is probably sufficiently good to infer that the assumption made in calculating ΔH_{13} is correct. More convincing evidence is available from the simple reactions studied in dilute nitric acid. From (5) and (1*a*), using Delepine's value for ΔH_{1a},

(18) Hexamine$_{(s)}$ + HNO_3 (65%) = hexamine dinitrate$_{(s)}$; ΔH_{18} = − 28.7 kcal.

and

(19) Hexamine mononitrate$_{(s)}$ + HNO_3 (65%) = hexamine dinitrate$_{(s)}$; ΔH_{19} = − 15.7 kcal.

whence

(20) Hexamine$_{(s)}$ + HNO_3 (65%) = hexamine mononitrate$_{(s)}$; ΔH_{20} = − 13.0 kcal.

It seems improbable that ΔH_{20} and ΔH_{13} would agree as they do, unless the assumption underlying the calculation of ΔH_{13} (i.e. that the mononitrate is an intermediate in the Bachmann reaction) was justified. On the whole, it appears that much, if not all of the hexamine in the Bachmann reaction is converted to RDX by way of the mononitrate rather than the dinitrate. This conclusion would be in agreement with the earlier observation that the activation energy for the Bachmann conversion of hexamine dinitrate to RDX is significantly

greater than for the conversion of hexamine mononitrate under similar conditions (3).

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THE BIOGENESIS OF ALKALOIDS

VI. THE FORMATION OF HORDENINE AND N-METHYLTYRAMINE FROM TYRAMINE IN BARLEY[1]

By Edward Leete[2], Sam Kirkwood[3], and Léo Marion

ABSTRACT

Tyramine-α-C^{14}, synthesized from C^{14}-barium carbonate, was administered to sprouting barley and radioactive hordenine and N-methyltyramine isolated from the roots. Separation of these alkaloids by chromatography followed by degradation showed that all the activity was located in the α-carbon atom. The specific activity of the N-methyltyramine was about 10 times that of hordenine. From the results it is concluded that tyramine undergoes methylation in the barley root to N-methyltyramine and thence to hordenine.

It has been shown (13) that formate is utilized in barley roots for the production of the N-methyl groups of the alkaloid hordenine (N-dimethyltyramine). Preliminary experiments (13) have also indicated that although formate is also responsible for the formation of the methyl groups of choline, the latter is not involved in the methylation of hordenine. Quite recently Brown and Byerrum (3) have studied the synthesis of nicotine in *Nicotiana rustica* L., and their results seem to indicate that the role of formate consists in the production of the labile methyl group of methionine which subsequently undergoes transmethylation with nornicotine.

The isolation of N-methyltyramine from certain species of barley (12) provided evidence in favor of the assumption that the final step in the synthesis of hordenine by the plant was the N-methylation of tyramine. This assumption could be confirmed by feeding tyramine labelled with C^{14} to the plant and, after a suitable time, isolating the hordenine and determining whether it was labelled on the same carbon atom as in the administered tyramine.

Since tyramine and hordenine are chemically so similar it was essential to devise a method that would separate them completely in order to be sure that any activity found in the isolated hordenine was not due to a trace of the administered active tyramine. Paper chromatography was found to be an excellent method of distinguishing between these amines. Munier and Macheboeuf (19) have described the paper chromatography of various alkaloids, including hordenine. However chromatograms run with the solvents described by these authors failed to afford discrete separation of tyramine, hordenine, and N-methyltyramine. The last base was included in this test since it was found to occur with the hordenine in the roots of Charlottetown No. 80 barley which was the species under investigation. The best separation on untreated filter paper was achieved with *n*-butanol containing ammonia as the developing solvent. The pH of the solvent was found to influence the R_F values of the amines, and since filter paper buffered to a fixed pH had been useful in the

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separation of the solanaceous and ergot alkaloids (4), this technique was investigated. On carrying out a series of chromatograms on paper buffered at different pH values, varying degrees of separation were obtained. As was expected, with acidic paper all the amines had low R_F values while with strongly alkaline paper their R_F values all tended towards 1. The best separation of the amines was obtained with paper buffered at pH 8 and with *n*-butanol as the developing solvent. The alkaloids were detected by spraying the paper with Millon's reagent; as little as 5 μgm. could be detected. On a macro scale it was possible to effect separation by absorption chromatography on alumina, the tyramine being the most strongly absorbed and the hordenine least.

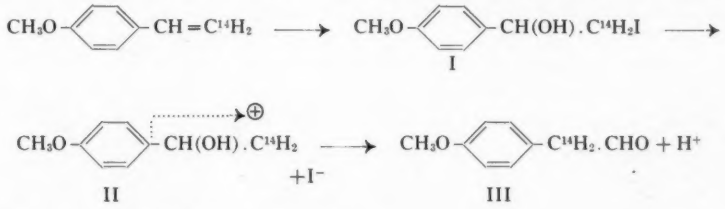
Barley was grown as previously described (13) and the roots harvested when according to Raoul (20) they contained a maximum amount of hordenine (11 days). On subjecting the crude alkaloids from the roots to chromatography it was found that an appreciable quantity of N-methyltyramine was present as well as the hordenine, there being about half as much N-methyltyramine as hordenine. Presumably previous workers have failed to isolate this alkaloid when hordenine was present because of the similarity of its properties to those of hordenine.

Tyramine-α-C^{14} was synthesized by a modification of the method of Koessler and Hanke (14). C^{14}-barium carbonate was converted to C^{14}-potassium cyanide (1, 6, 9) which was reacted with ethyl *p*-chloromethylphenyl carbonate (24) to give *p*-hydroxybenzylcyanide. This product was reduced with hydrogen over Raney nickel, in the presence of ammonia to suppress the formation of secondary amine (23), and the isolated tyramine was purified by sublimation and converted to the water-soluble hydrochloride which was used for feeding to the plant.

Feeding inactive tyramine hydrochloride to the plant had no visible effect on the growth of the barley or on the quantities of hordenine and N-methyltyramine isolated from the roots. On adding active tyramine hydrochloride to the barley on the sixth day of germination followed by isolation of the alkaloids on the 11th day, radioactive hordenine and N-methyltyramine were obtained; no tyramine was detected. Derivatives of the hordenine and N-methyltyramine retained the same specific activities as the parent alkaloids (Table II) showing that their activity was not due to any impurity. In order to determine the localization of the radioactivity, the hordenine was degraded by essentially the same methods used by Leger (16) in the original work on the constitution of hordenine. O-Acetylhordenine when oxidized with potassium permanganate gave rise to inactive *p*-acetoxybenzoic acid, indicating that the radioactivity resided either in the α-carbon atom or in the N-methyl groups or both. Hordenine methiodide was converted to the O-methyl ether and distillation of the corresponding quaternary hydroxide (Hofmann degradation) gave trimethylamine and *p*-vinylanisole. The trimethylamine was isolated as its platinichloride and was found to be inactive. The *p*-vinylanisole was not isolated as such owing to its lack of stability, but was immediately oxidized with yellow mercuric oxide and iodine (17) to homoanisaldehyde which was characterized as the oxime. This had the same specific activity as the original hordenine. All the foregoing

results seem to indicate that the activity resided entirely on the α-carbon atom of hordenine.

The active N-methyltyramine could not be oxidized to *p*-acetoxybenzoic acid since acetylation gave an ON-diacetyl derivative which was stable to oxidation. It was therefore converted to hordenine methiodide by refluxing with methyl iodide in the presence of sodium carbonate. After O-methylation the Hofmann degradation was carried out and it yielded trimethylamine which was converted to the platinichloride, and *p*-vinylanisole which was oxidized with yellow mercuric oxide and iodine. The product of the oxidation, homoanisaldehyde, was converted to the oxime and further oxidized with potassium permanganate. Rather surprisingly the anisic acid thus obtained was active and had the same specific activity as the original N-methyltyramine, apparently indicating that the activity in the N-methyltyramine was in the β-carbon atom adjacent to the benzene ring. However when a similar degradation was carried out on a sample of synthetic tyramine-α-C^{14}, active anisic acid was also obtained. Furthermore oxidation of the *p*-vinylanisole obtained from tyramine-α-C^{14} with potassium permanganate produced inactive anisic acid and active carbon dioxide. Thus, if it be assumed that no rearrangement takes place during the permanganate oxidation, it is obvious that a rearrangement had occurred during the conversion of *p*-vinylanisole to homoanisaldehyde oxime. This type of rearrangement was first observed by Tiffeneau (25) with substituted styrenes. The *p*-vinylanisole reacts with the mercuric oxide and iodine to give the iodohydrin (I) which by ionization of the iodine forms a carbonium ion (II) and this rearranges to homoanisaldehyde (III). The mechanism involving an intermediate π complex is discussed by Dewar (5). Hence, the radioactivity in both N-methyltyramine and



hordenine resides all in the α-carbon atom.

These results indicate that the tyramine has been utilized as such for the synthesis of N-methyltyramine and hordenine; the higher activity of the former is consistent with it being the intermediate in the formation of hordenine from tyramine. The roots from which the hordenine and N-methyltyramine had been extracted had a rather high activity suggesting that the hordenine might be converted to other substances which are utilized by the roots for their development. Its metabolism in the roots does not seem to be a general breakdown to simple carbon compounds containing one or two carbon atoms, for if this were the case one would expect these simple compounds to be utilized throughout the whole of the plant in other synthetic processes, whereas the leaves of the harvested barley were found to be completely inactive. Raoul (20) claimed that no

hordenine was present in the barley seeds. This has been confirmed and no trace of N-methyltyramine or tyramine was detected either. It seems highly likely that the source of tyramine in the roots is tyrosine since it is well established that this amino acid is converted by a variety of bacteria (4, 7, 8, 15, 18, 21) and in the kidney tissue of animals (10, 11, 22, 27) to tyramine. However Werle and Boden (26) were unable to detect an amino acid decarboxylase in yeast extracts. An investigation is at present proceeding of the metabolism of tyrosine in barley roots.

EXPERIMENTAL[4]

Paper Chromatography of Tyramine and its N-methyl Derivatives

The ascending method of paper chromatography (28) was used. Whatman No. 1 paper was cut into sheets 18 by 11 in., spots of the alkaloid solution were placed on the long edge about one inch from the bottom, 10 to 20 μgm. in a volatile solvent such as ethanol or methanol were in general used. The paper was stapled together at the shorter edge to give a cylinder 11 in. high, this was placed in a dish of the developing solvent in a closed container and left until the solvent had almost reached the top. The solvent front was marked and, after drying, the paper was sprayed with a solution of Millon's reagent (prepared by dissolving mercury (25 gm.) in concentrated nitric acid (25 cc.) and then diluting to 100 cc. with distilled water). The position of the alkaloids was shown by the formation of a red spot which slowly became brown and faded. The R_F values of these amines determined with a variety of solvents are shown in Table I.

TABLE I

R_F VALUES OF AMINES WITH VARIOUS SOLVENTS

Solvent mixture*	R_F value (at 25°)		
	Tyramine	N-Methyl-tyramine	Hordenine
Methylethyl ketone, water	0.074	0.053	Diffuse spot
Methylethyl ketone, 1% acetic acid	0.10	0.085	Diffuse spot
Ether, water	0.40**	0.48**	0.78**
n-Butanol, water	0.30	0.40	0.50
n-Butanol, 5% acetic	0.35	0.41	0.37
n-Butanol, 20% acetic	0.43	0.49	0.49
n-Butanol, 5*N* ammonia	0.74	0.85	0.95

**The organic solvent being in equilibrium with the second mentioned aqueous solution at 25°.*
***Elongated bands were produced and the maximum distance moved was measured to determine the R_F values.*

Buffered filter paper was obtained by dipping the paper in buffer solutions and then removing the surplus solution by pressing between blotting paper. The pH range 2.2 to 8.0 consisted of mixtures of 0.2 *M* disodium phosphate and 0.1 *M* citric acid; the range from 8.0 to 10.0, of mixtures of 0.1 *M* sodium hydroxide and 0.1 *M* boric acid. The paper was dried at room temperature. The results obtained with this buffered paper are shown graphically in Fig. 1,

[4] *All melting points are corrected.*

n-butanol saturated with water being the developing solvent. The most discrete separation was obtained with paper of pH 8, when the R_F values for tyramine, N-methyltyramine, and hordenine were 0.33, 0.44, and 0.83 respectively.

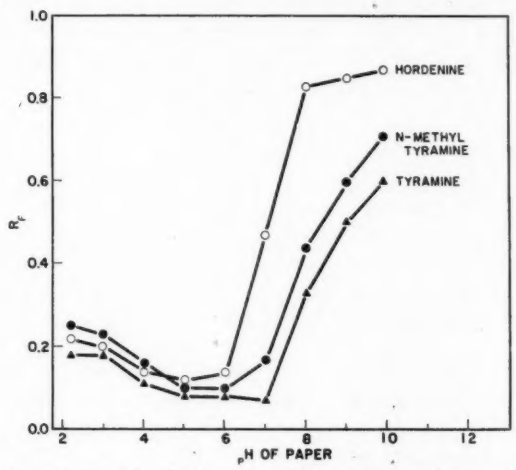


FIG. 1. The R_F values of hordenine, N-methyltyramine, and tyramine at various pH conditions.

Investigation of the Alkaloids from the Roots of Germinating Barley

Charlottetown No. 80 barley (720 gm.) was grown as previously described (13) and harvested on the 11th day of sprouting. The crude alkaloid fraction was obtained by an established method (12), consisting in extracting the dried roots with methanol, evaporating to dryness, dissolving the residue in 2*N* sulphuric acid, extracting this with ether to remove nonbasic products, alkalizing the sulphuric acid solution with ammonia, and extracting with ether. The alkaloids were extracted from this ether extract with sulphuric acid, the acid solution alkalized again with ammonia, and extracted with ether. The residue (0.554 gm.) left after the evaporation of this final ether extract was a brown semisolid mass which was dissolved in 10 cc. of methanol and an aliquot part containing about 50 μgm. was subjected to paper chromatography along with control samples of hordenine, N-methyltyramine, and tyramine. It was found that with a variety of developing solvents and with paper of different pH spots were obtained from this crude extract corresponding in position to hordenine and N-methyltyramine. From the density of the spots it was estimated that there was about twice as much hordenine as N-methyltyramine. No trace of tyramine was detected.

The methanol solution of the crude alkaloids was diluted with 200 cc. of benzene and chromatographed on alumina (activity 0-1). The composition of the eluates was determined by taking a few drops of the eluate and chromatographing it on paper along with controls. Hordenine was eluted with a 10% solution of methanol in benzene, the N-methyltyramine remaining on the

column, this was eluted by washing the column with pure methanol. Combination of the eluates yielded 0.216 gm. of hordenine and 0.080 gm. of N-methyltyramine (in a repeat experiment 0.241 gm. of hordenine and 0.097 gm. of N-methyltyramine were obtained from 720 gm. of barley). The identity of these fractions was confirmed by the preparation of hydrochlorides and picrates which were not depressed by admixture with the corresponding authentic derivatives of hordenine and N-methyltyramine.

Tyramine-α-C^{14}

Barium C^{14}-carbonate (12.087 mgm. with a total activity of 3.95×10^8 disintegrations per minute) was converted to hydrogen cyanide by fusing with sodium azide and then to potassium cyanide by absorption in potassium hydroxide as previously described (1, 6). The product was diluted with inactive potassium cyanide to give a total amount of 1.068 gm. ethyl *p*-chloromethylphenyl carbonate (24) (b.p. 112-5° at 0.8 mm., 3.522 gm.), was dissolved in ethanol (5 cc.), and added to the potassium cyanide dissolved in a minimum of water. The mixture was refluxed for two hours, the potassium chloride filtered off, and the filtrate evaporated to dryness *in vacuo*. The viscous residue was dissolved in ethanol (10 cc.) and refluxed with 2 cc. of a settled suspension of Raney nickel in ethanol for one hour. The filtered solution was concentrated *in vacuo* to give crude *p*-hydroxybenzylcyanide as a semisolid mass (in preliminary experiments with inactive cyanide it was obtained crystalline). The nitrile was dissolved in ethanol (3 cc.) and 3 cc. of a settled suspension of Raney nickel added, followed by liquid ammonia (3 cc.). The mixture was hydrogenated at 110° and 140 atmospheres in a high pressure autoclave for 15 hr. The product which was light brown in color was dissolved in ethanol, filtered, and then evaporated to dryness. The residue was dissolved in 2*N* hydrochloric acid (100 cc.) and extracted with ether, the aqueous layer was alkalized with ammonia and extracted with ether in a continuous extractor. The dried ether extract was evaporated to yield a viscous oil which was distilled at 120-130° at 10^{-3} mm. to yield tyramine-α-C^{14} as a white crystalline solid (0.677 gm., 30% yield from the potassium cyanide). A portion when crystallized from ethanol separated as colorless plates, m.p. 161.5-162.5° (Barger (2) reported m.p. 161°). The rest of the tyramine (0.521 gm.) was dissolved in ethanol and hydrochloric acid added to the solution when tyramine hydrochloride immediately separated out. It was crystallized from ethanol to yield colorless plates m.p. 273.5-275° (0.226 gm.). Found: C, 55.44; H, 6.63; N, 7.95; Cl, 20.85. Calcd. for $C_8H_{12}ONCl$: C, 55.34; H, 6.97; N, 8.07; Cl, 20.43%. The tyramine hydrochloride had a specific activity of $1.27 \pm .01 \times 10^5$ disintegrations per minute per mgm.[5] or $2.20 \pm 0.02 \times 10^7$ disintegrations per minute per millimole. By adding inactive tyramine hydrochloride to the mother liquor and concentrating the solution, further tyramine hydrochloride was obtained with a lower specific activity.

[5] *This activity and all subsequent ones were determined on thin samples with a Radiation Counters Laboratory "Nucleometer" making the usual corrections for self-absorption etc.*

Administration of Tyramine-α-C^{14} Hydrochloride to the Barley and Isolation of the Alkaloids

Barley (720 gm.) was grown as previously described and on the sixth day of sprouting radioactive tyramine hydrochloride (186.1 mgm. having a total activity of 2.36×10^7 disintegrations per minute and a specific activity of 2.20×10^7 disintegrations per minute per millimole) was fed to the barley in 600 cc. of distilled water. The addition of the tyramine did not affect the normal growth of the barley. On the 11th day of sprouting the roots were harvested and extraction as previously described (13) yielded the crude alkaloid fraction (0.491 gm.) with an activity of 2090 disintegrations per minute per mgm. The dried shoots were found to be completely inactive. The roots (74.5 gm.) which had been extracted with boiling methanol for 48 hr. had a residual activity of 106 disintegrations per minute per mgm. The crude alkaloid extract was dissolved in methanol (10 cc.) and several aliquot parts were chromatographed on paper of pH 8. Part of the paper was sprayed with Millon's reagent to detect the alkaloids. A photograph of the sprayed paper is shown in Fig. 2. The crosses along the line *A B* are the spots where the alkaloid solutions were initially placed, *C D* is the final solvent front. The developed chromatogram from another spot, not sprayed with Millon's reagent, was cut into strips 1 cm. wide. The strips were extracted with methanol and evaporated on to separate aluminum disks. The activity of these extracts (the actual counts observed above the background with the Nucleometer without any corrections) plotted against the distance of the strip from the initial spot of alkaloid solution is shown in Fig. 3.

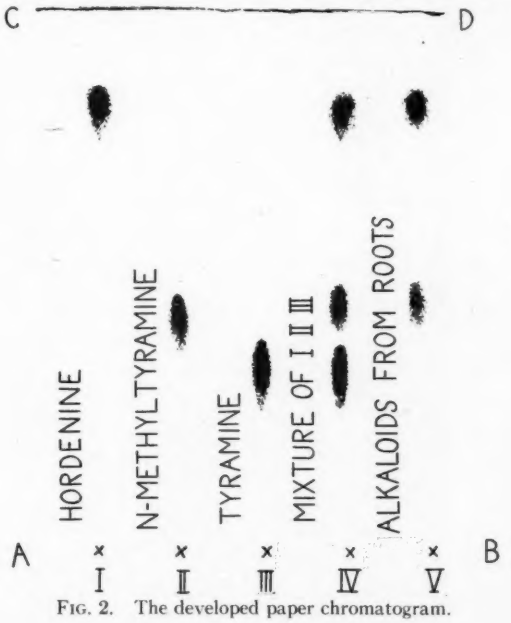


FIG. 2. The developed paper chromatogram.

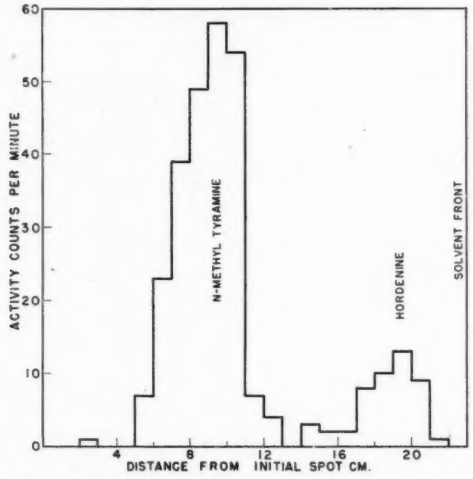


FIG. 3. Radioactivity of strips of the paper chromatogram.

It is seen that the positions of activity correspond to the positions of N-methyltyramine and hordenine as detected by Millon's reagent. After dilution of the methanol solution of the alkaloids with benzene it was chromatographed on alumina to yield 0.137 gm. of hordenine and 0.087 gm. of N-methyltyramine. The hordenine was diluted with 2.000 gm. of inactive hordenine and distilled at 130-140° at 10^{-3} mm. The crystalline distillate was crystallized from benzene–petroleum ether to give 1.8655 gm. By determining the activity of this diluted hordenine it was calculated that the hordenine isolated from the plant had an activity of 1.08×10^5 disintegrations per minute per millimole. In a similar way the N-methyltyramine was diluted with 1.865 gm. of inactive N-methyltyramine, distilled *in vacuo* 140-150° at 10^{-3} mm., and the distillate crystallized from anisole to yield 1.7147 gm. The activity of this diluted sample indicated that the N-methyltyramine from the plant had an activity of 1.04×10^6 disintegrations per minute per millimole. All subsequent derivatives and degradation products of these alkaloids were obtained from these diluted samples and their specific activities multiplied by the dilution factor.

Derivatives of the Active Hordenine

Picrate: small yellow prisms from aqueous ethanol, m.p. 140-140.5°.

Hydrochloride: colorless needles from ethanol, m.p. 179-180°.

Platinichloride: This was obtained by dissolving the hordenine hydrochloride in 5*N* hydrochloric acid and then adding an excess of chloroplatinic acid. The orange precipitate was crystallized from hydrochloric acid containing chloroplatinic acid; hordenine platinichloride separated as orange plates, m.p. 115-116°. Found: C, 31.92; H, 4.47; Pt, 26.9%. Calcd. for $(C_{10}H_{15}ON)_2.H_2PtCl_6$: C, 32.44; H, 4.35; Pt, 26.37%.

Methiodide: Active hordenine (1.300 gm.) was refluxed with methyl iodide (6 cc.) in methanol (25 cc.) for 15 min., and the solution evaporated to a small

bulk. The crystalline methiodide which separated was filtered and washed with ether–methanol, yield, 2.247 gm., m.p. 232-233°.

O-Methylhordenine methiodide: Hordenine methiodide (2.000 gm.) was dissolved in 10 cc. of a 10% aqueous solution of sodium hydroxide and dimethyl sulphate (1.6 cc.) was added with stirring. After stirring at room temperature for six hours, acetic acid (6 cc.) and sodium acetate (3.0 gm.) were added to the solution which was then concentrated to 5 cc. On cooling the O-methyl ether separated as colorless microscopic prisms (2.008 gm.) having no definite melting point.

Hofmann Degradation

The active O-methylhordenine methiodide (1.50 gm.) was dissolved in water (30 cc.) and silver hydroxide (obtained from 1.0 gm. of silver nitrate and sodium hydroxide) was added. After stirring for five hours at room temperature in the dark, the mixture was filtered to remove the silver iodide and the filtrate was introduced into a sublimation bulb. The solution was evaporated almost to dryness under reduced pressure and the sublimation bulb was then connected to a high vacuum system through two traps, the first cooled to 0° in ice and the second to −70° in a mixture of dry ice and acetone. The bulb was heated in an air bath to 120-130° when the *p*-vinylanisole distilled; most of it condensed in the first trap, while the second trap collected the trimethylamine. The contents of the traps were treated with dilute hydrochloric acid and the spherical droplets of *p*-vinylanisole extracted with ether (20-30 cc.).

The hydrochloric acid solution was evaporated to dryness and the white crystalline residue dissolved in ethanol, filtered, and added to an excess of chloroplatinic acid in ethanol. The pale orange precipitate was filtered (0.198 gm.) and crystallized from aqueous ethanol. Trimethylamine platinichloride separated as orange prisms, m.p. 231° (dec.).

The ether solution of *p*-vinylanisole was stirred with yellow mercuric oxide (1.5 gm.) and iodine (1.5 gm.) added. After two hours the solution was filtered and the brown filtrate was shaken with aqueous sodium thiosulphate to remove excess iodine. The pale yellow ether solution containing homoanisaldehyde was shaken with a solution of sodium bisulphite (3.0 gm.) in water (10 cc.). The bisulphite derivative, which separated as an amorphous yellow precipitate (0.142 gm.), was suspended in water (1 cc.) and to the suspension was added a solution of hydroxylamine hydrochloride (0.1 gm.) and sodium carbonate (0.1 gm.) in water (1 cc.). The mixture was stirred at room temperature; it was semisolid at first, but gradually became crystalline. The oxime was filtered and crystallized from aqueous methanol from which it separated as glistening plates, m.p. 116-119°, not depressed in admixture with homoanisaldehyde oxime, m.p. 119-120°.

Oxidation of Hordenine

Hordenine (0.102 gm.) was warmed with acetic anhydride (1 cc.) for three hours at 100°. The solution was diluted with water (10 cc.) and almost neutralized with potassium carbonate. Potassium permanganate (25 cc. of a 3% aqueous

solution) was added to the solution at 60-70°. After keeping for 15 min. at this temperature the excess permanganate was destroyed by addition of a few drops of ethanol and the manganese dioxide filtered. The alkaline filtrate was acidified with concentrated hydrochloric acid and the evolved carbon dioxide passed into a barium hydroxide solution. The precipitated barium carbonate was filtered, dried, and its activity determined. The total activity in the isolated barium carbonate was found to be 517 disintegrations per minute. If all the activity in the original amount of hordenine had been transferred to the barium carbonate an activity of 4400 disintegrations per minute would have been expected.

The acidified solution was extracted with ether, the extract dried over sodium sulphate and evaporated to dryness. There was left a colorless residue which crystallized from water as glistening colorless plates (0.033 gm.), m.p. 188-189°, not depressed in admixture with *p*-acetoxybenzoic acid, m.p. 193.5-194°. Found: C, 59.74; H, 4.64%. Calcd. for $C_9H_8O_4$: C, 60.00; H, 4.48%. The activities of the derivatives and degradation products of hordenine obtained from the plant are summarized in Table II.

TABLE II

ACTIVITIES OF THE DERIVATIVES AND DEGRADATION PRODUCTS OF HORDENINE

Compound	Disintegrations per minute per millimole
Hordenine	1.08×10^5
Hordenine picrate	1.07×10^5
Hordenine hydrochloride	1.04×10^5
Hordenine platinichloride	0.99×10^5
Hordenine methiodide	1.09×10^5
O-Methylhordenine methiodide	1.03×10^5
Trimethylamine platinichloride	0
Homoanisaldehyde oxime	0.96×10^5
p-Acetoxybenzoic acid	0

Derivatives and Degradation of Active N-methyltyramine

Picrate: yellow prismatic plates from aqueous ethanol, m.p. 149°.

Hydrochloride: colorless plates from ethanol, m.p. 148°.

Platinichloride: microscopic orange prisms, m.p. 208-209° (dec.).

Conversion to hordenine methiodide: A mixture of N-methyltyramine (1.300 gm.), sodium bicarbonate (0.74 gm.), methyl iodide (6 cc.), and methanol (20 cc.) was refluxed, with stirring, for two hours. It was filtered hot and the insoluble material washed well with methanol. The combined filtrate and washings were evaporated to a small bulk and allowed to cool when hordenine methiodide crystallized (2.018 gm.), m.p. 232°. Hordenine methiodide was methylated and degraded by the method already described, to homoanisaldehyde oxime and trimethylamine.

Oxidation of Homoanisaldehyde Oxime Derived from N-methyltyramine

The active oxime (9.17 mgm.) together with inactive oxime (98.5 mgm.) was dissolved in water (20 cc.) containing sodium hydroxide (0.1 gm.). Potassi-

um permanganate (15 cc. to a 3% aqueous solution) was added and the resulting solution refluxed for 30 min. Alcohol was then added to destroy the excess permanganate and the mixture filtered. The filtrate was evaporated to a small bulk and acidified with hydrochloric acid when a white crystalline precipitate separated (34.3 mgm.), m.p. 183-184°, undepressed in admixture with authentic anisic acid (m.p. 184°).

To a solution of the anisic acid (28.2 mgm.) obtained from the oxidation in 10% aqueous sodium hydroxide (1 cc.), *p*-bromophenacyl bromide (52 mgm.) in ethanol (10 cc.) was added and the mixture refluxed for one hour. Most of the alcohol was then evaporated and on cooling the *p*-bromophenacyl derivative of anisic acid crystallized (32.6 mgm.), m.p. 150-151°, not depressed in admixture with an authentic specimen of the derivative, m.p. 151-152°.

Degradation of Tyramine-α-C^{14}.

The degradation experiments were carried out on a sample of the product synthesized for administration to the plant and diluted with inactive tyramine.

Tyramine (1.226 gm.), sodium bicarbonate (1.70 gm.), and methyl iodide (6 cc.) were added to methanol (20 cc.) and refluxed for three hours with stirring. Hordenine methiodide was isolated from the reaction mixture as described in its preparation from N-methyltyramine, yield 2.413 gm. This was methylated and degraded as before to trimethylamine and *p*-vinylanisole which was in part converted to homoanisaldehyde oxime.

The remainder of the *p*-vinylanisole (0.120 gm.), freshly distilled from the Hofmann degradation, was suspended in water (10 cc.) containing sodium hydroxide (0.1 gm.) and to the suspension potassium permanganate (30 cc. of a 3% aqueous solution) was added. After allowing to stand two hours at room temperature the mixture was refluxed for 30 min. The excess permanganate was destroyed by the addition of a little ethanol and the reaction mixture filtered. The filtrate was acidified with hydrochloric acid and the evolved carbon dioxide

TABLE III

ACTIVITIES OF DERIVATIVES AND DEGRADATION PRODUCTS OF N-METHYLTYRAMINE AND OF TYRAMINE-α-C^{14}

Compound	Disintegrations per minute per millimole	
	From N-methyltyramine	From tyramine-α-C^{14}
N-Methyltyramine	1.04×10^6	
N-Methyltyramine picrate	1.14×10^6	
N-Methyltyramine hydrochloride	1.13×10^6	
N-Methyltyramine platinichloride	1.05×10^6	
Hordenine methiodide	1.11×10^6	2.00×10^5
O-Methylhordenine methiodide	1.15×10^6	1.92×10^5
Trimethylamine platinichloride	0	0
Homoanisaldehyde oxime	1.01×10^6	2.01×10^5
Anisic acid (from oxidation of homoanisaldehyde oxime)	1.01×10^6	1.97×10^5
p-bromophenacyl deriv.	0.98×10^6	1.91×10^5
Anisic acid (from oxidation of *p*-vinylanisole)		0
p-bromophenacyl deriv.		0

absorbed in barium hydroxide. The activity of the isolated barium carbonate accounted for 45% of the activity originally present in the *p*-vinylanisole. The acidified solution on evaporation yielded anisic acid (0.053 gm.) which was converted to the *p*-bromophenacyl derivative.

The activity of the derivatives and degradation products of the N-methyltyramine and of tyramine-α-C^{14} are summarized in Table III.

Extraction of Barley Seeds

Barley seeds were ground in a Wiley mill and the ground product (300 gm.) was extracted with methanol for 48 hr. in a Soxhlet extractor. The extract, on distillation *in vacuo* to remove the methanol, left a pale yellow viscous residue (23.2 gm.). This when subjected to the same treatment as described for the crude extract of the roots gave a final ether extract which on evaporation yielded a pale yellow viscous liquid (0.204 gm.). An aliquot part of this liquid was chromatographed on paper of pH 8 along with controls of hordenine, N-methyltyramine, and tyramine, but no trace of any of these alkaloids was detected.

ACKNOWLEDGMENT

The authors are indebted to Mr. R. B. MacLaren of the Experimental Station, Charlottetown, P.E.I., for supplying the barley used in these experiments, and to Dr. R. E. Deriaz, at the time National Research Laboratories of Canada Fellow, who prepared the tyramine-α-C^{14}.

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PITHECOLOBINE, THE ALKALOID OF *PITHECOLOBIUM SAMAN* BENTH. I[1]

By K. Wiesner, D. M. MacDonald,[2] Z. Valenta, and R. Armstrong[3]

ABSTRACT

Pithecolobine, $C_{22}H_{46}N_4O_2$, has a lactam group, one primary and two secondary amino groups, and a hydroxyl group. Lithium aluminum hydride converts it into a monocyclic saturated compound, desoxypithecolobine, $C_{22}H_{48}N_4$. Hofmann degradation of this compound gives tetramethylputrescine, trimethyl amine, a doubly unsaturated base $C_{16}H_{31}N$ with a terminal methylene group, and a base $C_{16}H_{34}N_2$. Heating with selenium yields a hydrocarbon, $C_{12}H_{24-26}$, with a sequence of six or more CH_2 groups. A crystalline oxygen-free compound with two nitrogens (m.p. 94°C.) is also obtained, the ultraviolet spectrum of which is almost identical with aminopyridine.

Some time ago we obtained, through the courtesy of Dr. R. Tondeur of the Institut National pour l'Étude agronomique du Congo Belge, a large amount of the bark of the shade tree *Pithecolobium saman* Benth.

From this bark an alkaloid had been already reported by Greshoff (1) who, however, did not purify or analyze it. Subsequently, Van Itallie (2) claimed to have isolated two bases, $C_{17}H_{36}N_3O$ and $C_8H_{17}NO$, from the same source. The material Van Itallie had in his hands was obviously impure, and no convincing evidence of a separation into two distinct compounds was presented.

We have isolated by methods described in the experimental part about 1% of crude base, which, after chromatographic purification, slowly crystallized, but could not be recrystallized from solvents.

The only derivative found to crystallize easily was the picrolonate, which was extremely insoluble in methanol and recrystallized from acetone–methanol mixtures to a melting point of 135° C. The analyses of this picrolonate (although there is hardly any doubt that it behaves as a homogeneous substance) showed fluctuations, and it was difficult to decide for certain between the possibilities of a tripicrolonate of the formulae $C_{22}H_{48}N_4O_3$ or $C_{22}H_{46}N_4O_2$ and two similar formulae possessing one $-CH_2$ more. The C_{23} formulation was later excluded on the basis of analyses of desoxypithecolobine (*vide infra*).

The analysis of the free base liberated from the picrolonate showed, if the base was sublimed at 135° C., reasonable agreement with the N_4O_3 formulation. The base distilled in high vacuum in a collar-flask at about 230° C. with some decomposition, and the distillate showed approximate agreement with the N_4O_2 formula.

At this stage we decided to prove as rigorously as possible the homogeneous character of our tripicrolonate. The base was subjected to a twofold countercurrent distribution; the peak of the first distribution was redistributed in 25 funnels giving a single peak with only minor impurities (see Fig. 1).

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Contribution from the Chemistry Laboratories of the University of New Brunswick.
[2] *Holder of an N.R.C. Fellowship.*
[3] *Holder of a Beaverbrook postgraduate Scholarship.*

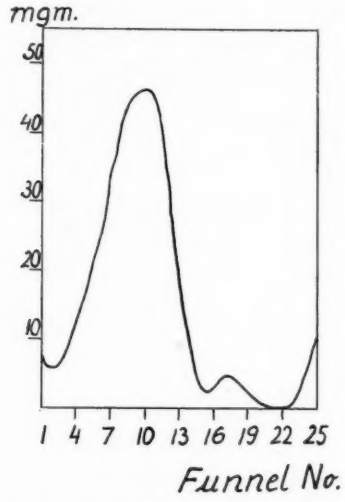

FIG. 1. Distribution curve of pithecolobine.

The peak fraction of this second distribution curve was converted to the tripicrolonate, and this derivative showed complete identity of properties and analyses with our previous samples.

If pure pithecolobine is heated for some time with potassium bisulphate it gives a tripicrolonate identical in all respects with pithecolobine tripicrolonate, but it checks reproducibly and perfectly to a tripicrolonate of formula $C_{22}H_{46}N_4O_2$.

The base liberated from this picrolonate and sublimed at 135° C. also checked to the same formula.

In view of the identity of the tripicrolonates, it is doubtful whether there is any significance, other than analytical difficulties, to be attached to the previously observed fluctuations of analyses, and at present we are of the opinion that $C_{22}H_{46}N_4O_2$ represents the correct formula of pithecolobine.

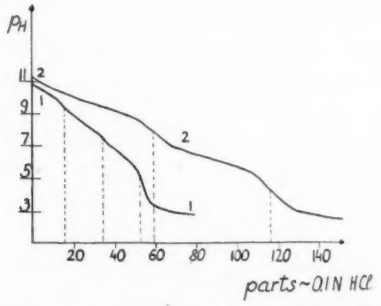

FIG. 2. Titration curves: 1. pithecolobine; 2. desoxypithecolobine.

This view is also corroborated by the analyses of desoxypithecolobine (*vide infra*).

Pithecolobine has three basic nitrogens, as shown by the titration curve (Fig. 2).

The fourth nitrogen is present in the form of an amide group, as judged by the infrared spectrum, which shows a strong band at 1650 cm.$^{-1}$ (Fig. 3).

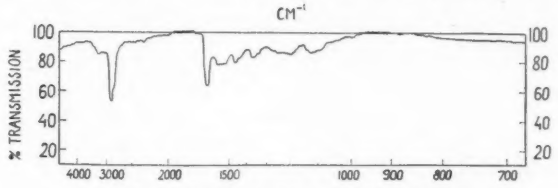

FIG. 3. Infrared spectrum of pithecolobine.

As pithecolobine does not absorb any hydrogen on catalytic hydrogenation, it must be monocyclic. The Van Slyke determination shows one primary amino group. Pithecolobine gives a neutral triacetate; it can therefore be concluded that it has one primary and two secondary amino groups.

There are no methoxyl groups and N-alkyl determination shows only a trace. (This might be caused by the structure $> N-(CH_2)_4-N <$ present in the compound (*vide infra*).)

Hydrolysis with concentrated hydrochloric acid cleaved the amide group. The hydrolysis mixture was extracted from both acidic and alkaline solution with chloroform and not a trace of either acidic or basic material was obtained. Also, steam distillation from alkaline solution did not yield a significant amount of a volatile amine. The product is an amino acid, which gives a jellylike, intractable hydrochloride, and an oily ester, which polymerizes on attempted distillation. Thus in spite of the difficulties to characterize the product, it can be concluded that the amide group is in a ring. Reduction of pithecolobine with lithium aluminum hydride gives a compound, desoxypithecolobine ($C_{22}H_{48}N_4$), characterized as the beautifully crystalline tetrahydrochloride and tetrapicrate. The infrared spectrum (Fig. 4) shows the disappearance of the amide group.

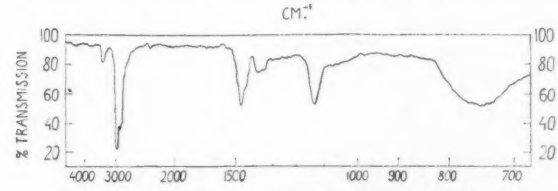

FIG. 4. Infrared spectrum of desoxypithecolobine.

The titration curve (Fig. 2) distinctly shows two separate steps of identical height. This clearly demonstrates the correctness of our formulation with four nitrogens, as a formula with two nitrogens is out of the question in view of the

boiling point. Desoxypithecolobine is saturated to platinum oxide in acetic acid, and therefore it is likely to be monocyclic. It gives a neutral acetyl derivative, showing that the lactam group of pithecolobine has been converted to a secondary amino group. The second oxygen of pithecolobine must have been in a hydroxyl group, as the four hydrogens missing to make up a completely saturated formula have already been accounted for by the lactam group, and as the oxygen has been removed without loss of carbon. The elimination of this oxygen by lithium aluminum hydride indicates its special position in pithecolobine.

Desoxypithecolobine was methylated with formaldehyde and formic acid, giving a compound, $C_{27}H_{58}N_4$, and therefore gaining five methyl groups in conformity with the assumption of three secondary and one primary amino groups. This compound gave a methohydroxide, which underwent the Hofmann degradation with the formation of tetramethylputrescine, identified with an authentic specimen by mixed melting point of picrates and infrared spectra of hydrochlorides.

The higher boiling products of this Hofmann degradation were a complex mixture of liquid bases, which could not be separated.

This mixture was once more converted into methohydroxides and subjected to a Hofmann degradation. In this step trimethylamine was identified as the picrate.

From the mixture of higher boiling bases one was separated in comparatively good yield by virtue of the solubility of its hydrochloride in chloroform.

The hydrochloride of this base and the free base check to $C_{15}H_{29}N$. The base appeared homogeneous, since all fractions of a careful Craig-column distillation had the same properties. The base has a pK of 7.49 and consumes two moles of hydrogen on hydrogenation. On ozonolysis a quantitative yield of the formaldehyde-dimedone compound was obtained, showing the terminal position of one of the double bonds. Hydrogenation of the base showed an uptake of two moles of hydrogen.*

From the mixture of bases obtained in the second step of the Hofmann degradation a picrolonate was isolated in a low yield checking for $C_{36}H_{50}N_{10}O_{10}$. This is a dipicrolonate corresponding to a base $C_{16}H_{34}N_2$.

Our further program is the elucidation of the structure of the $C_{16}H_{31}N$ base. There is some indirect evidence that there are 12 carbons of this compound in a chain. Treatment of desoxypithecolobine with selenium gave a hydrocarbon which checks for $C_{12}H_{24}$ or $C_{12}H_{26}$. The infrared spectrum of this hydrocarbon

*NOTE ADDED TO PROOF: *Further Hofmann degradation of the tetrahydro base gave a hydrocarbon, $C_{12}H_{24}$, and n-propyldimethylamine, the latter being identified with an authentic specimen. This evidence indicates that the original base must have been $C_{16}H_{31}N$ (Calculated: C, 80.94; H, 13.12; N, 5.90%), and indeed the analyses of the middle fractions of the Craig-column distillation agree well with this formulation (cf. Experimental Part).*

The $C_{12}H_{24}$ hydrocarbon absorbed one mole of hydrogen to give a saturated hydrocarbon, $C_{12}H_{26}$, the infrared spectrum of which was "almost identical" with n-dodecane. Indications are, therefore, that the chain is slightly branched.

Since account has now been made of all but three carbons of desoxypithecolobine, conclusions concerning the general type of structure of desoxypithecolobine can be drawn. These will be presented in a forthcoming communication.

(Fig. 5) shows indications of double bonds. However, hydrogenation showed an uptake of only approximately a third of a mole of hydrogen.

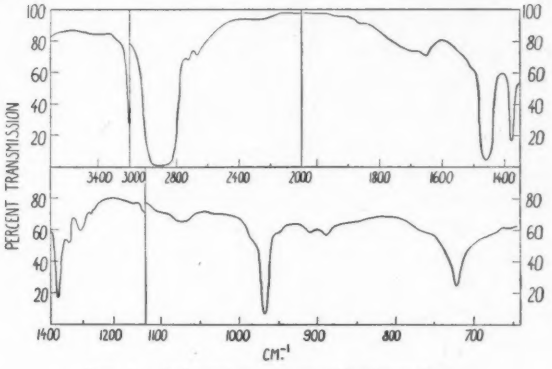

FIG. 5. Infrared spectrum of hydrocarbon.

The molecular weight determination gives a value between a C_{12} and C_{13} formula. Kuhn-Roth oxidation indicates a content of two C-methyl groups.

It is interesting to note that the infrared spectrum shows a strong peak at 722 cm.$^{-1}$, which could be ascribed to a sequence of six or more CH_2 groups.

It seems likely that the product is a C_{12} hydrocarbon with a certain amount of monounsaturated compound as contaminant. It also seems that this hydrocarbon contains the fragment of desoxypithecolobine which forms the carbon skeleton of the $C_{16}H_{31}N$ Hofmann degradation product.

A small amount of a crystalline compound was also isolated from the selenium

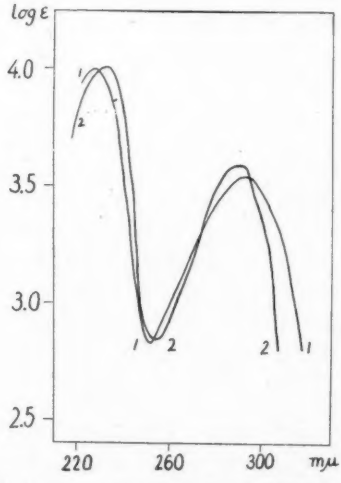

FIG. 6. Ultraviolet spectra: 1. compound m.p. 94°C.; 2. α-aminopyridine.

dehydrogenation of desoxypithecolobine. This was recrystallized only twice, followed by sublimation for analysis. In spite of the limited purification, it had a fairly sharp melting point of 93.5–94° C. The analysis approximates the formula $C_9H_{14}N_2$. The ultraviolet spectrum indicates an aromatic system substituted with an auxochromic group.

In Fig. 6 this spectrum is shown together with the spectrum of α-aminopyridine, with which it shows remarkable similarity.

We believe that the identification and the preparation of this compound in somewhat larger quantities should not prove too difficult. This compound, together with tetramethylputrescine and the $C_{16}H_{31}N$ base, will account for most of the carbon and nitrogen of desoxypithecolobine.

The information so far obtained on pithecolobine, while not as yet permitting us to put forward a definite structural formula, is nevertheless sufficient to show the remarkable and unusual character of this alkaloid.

EXPERIMENTAL PART

Isolation and Purification of Pithecolobine

The ground bark of *Pithecolobium saman* Benth. (500 gm.) was exhaustively percolated with petroleum ether, ether, and finally methanol.

The first two percolates gave 4.634 gm. and 1.735 gm. of a yellow semisolid oil, which was not investigated further. The methanol extract was evaporated almost to dryness, and the basic fraction was separated from it in the usual way, using chloroform for extraction. The brown viscous oil weighed 5.364 gm.

This was chromatographed on 200 gm. of basic Fisher alumina. Fractions of 500 ml. were collected. The first four fractions of pure chloroform eluted 143 mgm. of brown oil. The subsequent 14 fractions of 1% methanol in chloroform eluted 3.723 gm. of alkaloid, which was obtained as a pale yellow oil that crystallized but could not be recrystallized from solvents.

The last four fractions were taken with 5% methanol in chloroform and gave 288 mgm. of impure brown alkaloid.

Of the material eluted with 1% methanol in chloroform, 2.5 gm. were subjected to a nine-funnel countercurrent distribution between chloroform and phosphate–citrate buffer of pH 7.51 (450 ml. of each phase).

The result was as follows:

Funnel No.	Mgm. of substance
1	209
2	363
3	437
4	407
5	218
6	134
7	126
8	137
9	196

The material from funnels 2, 3, and 4 was colorless and crystalline.

The peak fraction 3 was redistributed in 25 funnels between chloroform and phosphate–citrate buffer of pH 7.66, using 100 ml. of each phase.

The distribution curve obtained (Fig. 1) indicates that one component predominates over only minor impurities.

The content of funnel 10 of the second distribution (46 mgm.) was treated with 92 mgm. of picrolonic acid in methanol. The extremely methanol-insoluble crystalline picrolonate was recrystallized five times from acetone–methanol. It melted at 134–135° C., and was dried for analysis at 80° C. in high vacuum for 24 hr. Other samples of picrolonate were prepared by treating the main chromatographic fraction or the peak fraction of the first distribution with picrolonic acid. All had the same properties except for small fluctuations of melting point of approximately 2° C.

	%C	%H	%N
Calculated for $C_{52}H_{72}O_{18}N_{16}$:	51.56	5.99	18.50
Calculated for $C_{52}H_{70}O_{17}N_{16}$:	52.43	5.92	18.81
Found:	52.48	6.21	18.13
	51.94	6.04	17.84
	52.02	6.02	17.99
	52.84	6.30	
	51.87	6.22	18.46
	52.32	6.17	18.08
	51.55	5.89	18.93

The fractions 8, 9, and 11 of the second distribution (total, 130 mgm.) were converted into the picrolonate and recrystallized to analytical purity. The picrolonate was then decomposed giving 72 mgm. of free base, which was sublimed at 135° C. (0.007 mm.) for analysis. It crystallized and melted at 67–69° C.

Calculated for $C_{22}H_{48}N_4O_3$: C, 63.42; H, 11.61; N, 13.45; (N) CH_3, 3.61; $-NH_2$, 3.85; 4 act. H, 0.98%.

Found: C, 63.76, 63.55; H, 11.90, 11.80; N, 12.38, 14.86; (N) CH_3, 1.66; $-NH_2$, 4.04; OCH_3, 0.0; act. H, "cold" 0.57; "warm" 0.91%.

A distillation of the base prepared in the same way gave the following results: the base boiled at 230° C. (outside temperature) in a collar-flask at 0.007 mm. The distillate showed distinct signs of decomposition and did not crystallize.

Calculated for $C_{22}H_{46}N_4O_2$: C, 66.27; H, 11.63; N, 14.04%.

Found: C, 70.19, 67.61; H, 11.91, 11.67; N, 13.20%.

Analysis of "Dehydrated" Base

Pure pithecolobine (200 mgm.) was heated with potassium bisulphate (400 mgm.) in an open flask for a few minutes to 120–180° C. The free base, separated in the usual way, gave a picrolonate, which was recrystallized five times for acetone–methanol. It melted at 137° C. and did not depress the melting point of pithecolobine picrolonate.

Calculated for $C_{52}H_{70}O_{17}N_{16}$: C, 52.43; H, 5.92; N, 18.81%.

Found: C, 52.57; H, 5.99; N, 18.83%.

The free base liberated from the pure picrolonate was sublimed for analysis at 135° C. in high vacuum.

Calculated for $C_{22}H_{46}N_4O_2$: C, 66.27; H, 11.63%.
Found: C, 66.05; H, 11.61%.

Acetylation of Pithecolobine

Pithecolobine (215 mgm.) was treated for 48 hr. with 2 ml. of acetic anhydride and 2 ml. of dry pyridine. After working up, 313 mgm. of crude, neutral oil was obtained. It was chromatographed on 9.5 gm. of neutral alumina. Fractions of 50 ml. were collected.

Absolute chloroform (400 ml.) eluted 160 mgm. of a clear, colorless, viscous oil, which was sublimed for analysis in high vacuum at 210° C.
Calculated for $C_{28}H_{52}N_4O_5$: C, 64.06; H, 10.01; N, 10.67%.
Found: C, 63.55; H, 10.04; N, 10.65%.

Desoxypithecolobine

Pithecolobine (1.5 gm.) was reduced with an excess of lithium – aluminum hydride in ether in the usual way. The product was 952 mgm. of a clear, basic liquid, which distilled at 178–185° C. (outside temperature) at 0.01 mm. in a collar-flask.

This material (37 mgm.) was treated with 92 mgm. of picric acid in methanol. The picrate precipitated immediately and was recrystallized five times from ethanol. It melted at 155° C. and was dried for analysis at 100° C. *in vacuo* for 24 hr.
Calculated for $C_{46}H_{60}N_{16}O_{28}$: C, 42.95; H, 4.72%.
Found: C, 43.08; H, 4.92%.

Another portion of the reduced base (443 mgm.) was converted to the hydrochloride and recrystallized from methanol–ether to the constant m.p. 245–248° C. It was dried for analysis at 100° C. in high vacuum.
Calculated for $C_{22}H_{52}N_4Cl_4$: C, 51.35; H, 10.19; N, 10.91; Cl, 27.57%.
Found: C, 51.24; H, 10.05; N, 10.74; Cl, 26.92%.

Desoxypithecolobine free base recovered from the analytically pure hydrochloride was fractionated in a collar-flask. The middle fraction boiled at 180° C. (outside) at 0.01 mm.
Calculated for $C_{22}H_{48}N_4$: C, 71.68; H, 13.12; N, 15.20; $(N)CH_3$, 4.08%.
Found: C, 71.85, 71.61; H, 12.77, 12.90; N, 15.44, 14.53; $(N)CH_3$, 3.11%.

Catalytic hydrogenation with platinum oxide in glacial acetic acid showed no uptake of hydrogen.

Acetylation of desoxypithecolobine with pyridine and acetic anhydride gave a quantitative yield of a neutral product, which was a glass and could not be purified for analysis.

Methylation of Desoxypithecolobine

Desoxypithecolobine (885 mgm.) was treated with 1.8 ml. of aqueous formaldehyde and 2.9 ml. of formic acid, and the mixture was refluxed for two hours. Then fresh formic acid (1 ml.) and formaldehyde (0.6 ml.) were added and the heating continued for six hours.

The basic fraction was isolated in the usual way giving a quantitative yield of a clear liquid.

The picrate of this compound melted at 108–109° C., and was dried at 70° C. in high vacuum for analysis.
Calculated for $C_{51}H_{70}N_{16}O_{28}$: C, 45.22; H, 5.21%.
Found: C, 45.15; H, 5.07%.

The analytically pure picrate was decomposed and the free base distilled for analysis in a collar-flask. The middle fraction boiled at 195–200° C. (outside) at 0.2 mm.
Calculated for $C_{27}H_{58}N_4$: C, 73.90; H, 13.32; N, 12.78%.
Found: C, 73.54; H, 12.87; N, 13.17%.

Hofmann Degradation

Methylated desoxypithecolobine (15.472 gm.) was dissolved in 700 ml. of absolute methanol and refluxed with 200 ml. of methyl iodide. The resulting solution was evaporated *in vacuo*. The methiodide was obtained as a sticky solid, which could not be recrystallized.

The methiodide (6.309 gm.) was dissolved in 40 ml. of water, an excess of freshly precipitated silver oxide was added, and the mixture was shaken overnight. After this the mixture was centrifuged and the precipitate washed with water. The combined supernatant solutions were evaporated to dryness at room temperature *in vacuo*.

The methohydroxide was slowly heated *in vacuo* in a round-bottomed flask equipped with a cold finger; volatile products were collected in two traps cooled by dry ice – acetone mixtures.

The decomposition started at 50–60° C. and was completed at 100° C. in a few hours.

The contents of the dry ice traps were washed out with alcoholic hydrochloric acid and evaporated to dryness. A crystalline hydrochloride (1.045 gm.) was obtained.

The content of the main decomposition flask was distilled *in vacuo*, and 1.613 gm. of a clear oil boiling at 120–136° C. at 0.5 mm. was obtained.

Three more experiments were performed with the same result.

The hydrochloride of the volatile amine was dissolved in water, made alkaline with sodium hydroxide, and distilled into a solution of picric acid in alcohol. The picrate crystallized immediately and was recrystallized from acetone to a constant m.p. of 201–202° C. A sample was dried for analysis in high vacuum at 70° C.
Calculated for $C_{20}H_{26}O_{14}N_8$: C, 39.87; H, 4.35; N, 18.60%.
Found: C, 39.91; H, 4.23; N, 18.54%.

The picrolonate, prepared in the same way and recrystallized from methanol, melted at 226–228° C.
Calculated for $C_{28}H_{36}N_{10}O_{10}$: C, 49.99; H, 5.40%.
Found: C, 49.63; H, 5.14%.

Synthetic tetramethyl tetramethylenediamine picrate melted alone and in admixture with the picrate of our degradation product at 200–201° C.

Analytically pure samples of both picrates were then decomposed and con-

verted to hydrochlorides. They were both recrystallized from alcohol–ether and melted alone and in admixture at 271–275° C. The infrared spectra of both hydrochlorides were identical.

The high-boiling base from the Hofmann decomposition refused to give crystalline derivatives, and proved, by countercurrent distribution, to be a complex mixture. Therefore, the high-boiling base mixture from three experiments (total, 6.771 gm.) was converted into methiodides and methohydroxides exactly as in the first step.

The second stage of the Hofmann decomposition was performed in the same way, high-boiling products being condensed by a cold finger and low-boiling products in a dry ice – acetone trap. From the trap 318 mgm. of a hydrochloride was obtained, which was converted to the picrate. It melted after recrystallization from methanol at 203–205° C., but was clearly distinct from tetramethyl tetramethylenediamine picrate by a large melting point depression and high solubility in methanol.

Calculated for $C_9H_{12}O_7N_4$: C, 37.50; H, 4.10; N, 19.44%.
Found: C, 37.77; H, 4.25; N, 19.47%.

The melting point of trimethylamine picrate was 201–203° C., and did not show a depression on admixture with the degradation picrate.

The high-boiling compounds, which remained in the decomposition flask and on the cold finger, were dissolved in chloroform and extracted three times with dilute hydrochloric acid. The acidic aqueous layer was then strongly basified and extracted with chloroform. After removing the chloroform, the residue was distilled in a collar-flask to give 0.691 gm. of an oil, b.p. 130–160° C. (outside) at 0.15 mm.

From this mixture of bases a crystalline picrolonate was isolated by fractional crystallization from methanol. It melted at 144–145° C., and was dried for analysis in high vacuum at 80° C.

Calculated for $C_{36}H_{50}N_{10}O_{10}$: C, 55.23; H, 6.44; N, 17.90%.
Found: C, 55.36; H, 6.73; N, 17.90%.

A small amount of a rather insoluble picrolonate melting at 193–194° C. was also isolated.

Calculated for $C_{35}H_{48}N_{10}O_{11}$: C, 53.56; H, 6.17; N, 17.85%.
Found: C, 53.36; H, 6.16; N, 17.89%.

The substance which remained in the chloroform layer during the original partition between chloroform and dilute hydrochloric acid has been shown to be a chloroform-soluble hydrochloride. The yield was 1.317 gm. It did not crystallize but could be distilled in a collar-flask, b.p. 130–150° C. (outside) at 0.05 mm.

Calculated for $C_{15}H_{30}NCl$: C, 69.34; H, 11.63; N, 5.39%.
Found: C, 69.13; H, 11.43; N, 5.43%.

To obtain the free base, the hydrochloride was dissolved in 5% sulphuric acid, the acidic layer was extracted with ether, then basified, and the precipitated base was extracted with ether. After evaporating the ether 0.734 gm. of a mobile oil was obtained. This compound distilled in a collar-flask at 120–130° C. (outside) at 0.85 mm.

It was fractionated for analysis and the middle fraction, which boiled at 119–123° C. (outside) at 1.4 mm., was analyzed.

Calculated for $C_{18}H_{29}N$: C, 80.63; H, 13.09; N, 6.28%.

Found: C, 81.08; H, 13.08; N, 6.48%.

The base refused to form any solid derivatives, and was therefore subjected to a careful fractionation in a Craig column. A sharply boiling middle fraction was taken for the fractionation.

Fraction	%C	%H	%N	Bath temp.	Jacket temp.	Pressure
1	80.63	13.11	6.40	177-178°C.	135-140°C.	2 mm.
2	81.12	13.23	6.22	179-182°	138-140°	"
3	81.25	13.13	5.92	180-184°	138-140°	"
4	80.43	13.17	6.09	184-187°	140°	"
5	80.60	12.98	6.03	188-190°	140°	"
6	80.70	12.78	6.39	190-200°	140-150°	"

Potentiometric microtitration of the base showed a pK of 7.49.

Hydrogenation with platinum oxide in glacial acetic acid indicated the presence of two double bonds.

Ozonolysis

The $C_{16}H_{31}N$ base from the second stage of the Hofmann degradation (198 mgm.) was ozonized for two hours at 0° C. in 30 ml. of absolute chloroform. The solution was then evaporated to dryness at room temperature *in vacuo*. After addition of 10 ml. of 5% sulphuric acid the solution was steam-distilled and 5 ml. of a 5% solution of dimedone was added. A precipitate was formed, which weighed 226 mgm. after one crystallization from alcohol and melted at 182–186° C. After three crystallizations the melting point was 191–192° C., alone and in admixture with the authentic dimedone-formaldehyde complex.

Selenium Dehydrogenation of Desoxypithecolobine

Desoxypithecolobine (4.043 gm.) was mixed with 11.5 gm. of red selenium and heated under nitrogen in a flask equipped with a reflux condenser. A colorless liquid started to reflux at 250° C., and the temperature was raised to 290° C. and maintained there for two hours. The material was then extracted in a Soxhlet apparatus with ether. The ether solution was filtered and washed with 5% sulphuric acid and water. After drying, the ether was distilled and the substance—a dark mobile oil—distilled in a collar-flask between 80–135° C. at 1 mm. The yield was 890 mgm. of a yellow-colored liquid. This was chromatographed on 35 gm. of alumina. Petroleum ether eluted 800 mgm. of slightly yellow oil, which was redistilled twice over sodium in a collar-flask, giving 500 mgm. of a colorless liquid boiling at 120–140° C. (outside) at 40 mm.

This product was fractionated in a Craig column.

Fraction	%C	%H	Bath temp.	Jacket temp.	Pressure
1	85.21	14.82	128°C.	73°C.	18 mm.
2	85.38	14.68	128-131°	72-75°	"
3	Infrared sample		131-136°	74-78°	"
4	84.42	14.59	133-150°	74-85°	"

Calculated for C_nH_{2n}: C, 85.62; H, 14.38%.
Calculated for $C_{12}H_{26}$: C, 84.61; H, 15.39%.
Calculated for the molecular weight of $C_{12}H_{24}$: 168.
Calculated for the molecular weight of $C_{13}H_{26}$: 182.
Found by the Rast method: 176.

The infrared spectrum of this compound is shown in Fig. 5.

Microhydrogenation in glacial acetic acid with Adams catalyst showed an uptake of 0.3 moles of hydrogen.

The sulphuric acid wash of the original ether extract was repeatedly extracted with chloroform, and the chloroform was evaporated to dryness. It yielded 178 mgm. of dark oil, which was chromatographed on 7.1 gm. of alumina. Absolute chloroform eluted 97 mgm. of oil, followed by 43 mgm. of crystals.

The crystalline material was recrystallized twice from ether to a melting point 93.5–94.0° C. This melting point might possibly have risen on further crystallization.

A sample was sublimed for analysis in high vacuum at 80° C.

Found: C, 70.97; H, 9.84; N, 18.17%.

The ultraviolet spectrum of the compound is given in Fig. 6.

The analyses were performed by the microanalytical laboratories of Dr. R. Dietrich, Zurich, and the University of Pittsburgh.

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TEMPERATURE INDEPENDENT FACTORS OF HYDROGEN ABSTRACTION REACTIONS IN THE GAS PHASE[1]

By S. Bywater and R. Roberts[2]

ABSTRACT

Temperature independent factors for a series of hydrogen abstraction reactions in the gas phase have been calculated using the absolute reaction rate theory of Eyring and co-workers. The calculated values have been compared with experimental values wherever possible. Reasonable agreement is obtained. The factors producing variations have been examined and the sources of error in this type of calculation are discussed.

INTRODUCTION

The increasingly accurate kinetic studies of gas phase reactions have made it possible to measure temperature independent factors of elementary reaction steps as well as activation energies. It is in principle also possible to calculate these so-called "A-factors" using the absolute reaction rate theory of Eyring (3) and co-workers. It is instructive to calculate pre-exponential factors for a series of hydrogen abstraction reactions and to compare the values with experiment wherever possible. In this way the factors which produce variations can be examined.

Evans and Szwarc (2) have calculated steric factors for a number of hydrogen abstraction reactions. Their formula however is only strictly applicable to the reaction between an atom and a diatomic molecule and thus the calculated values for reactions between more complex molecules cannot be considered accurate.

METHOD

According to the theory of absolute reaction rates (1) the rate constant (k) for a bimolecular reaction is given by:

$$k = \kappa e^2 \left(\frac{\mathbf{kT}}{\mathbf{h}}\right) e^{\Delta S_c^*/R} e^{-E/RT}$$

where E is the experimental activation energy; ΔS_c^* is the difference in entropy between the intermediate complex and reactants at unit concentration; κ is the so-called "transmission coefficient" which has a maximum value of unity and is usually close to this figure; and $\mathbf{k}$, $\mathbf{h}$ are the Boltzmann and Planck constants respectively.

The problem is to calculate ΔS_c^* for a series of reactions:

$$H' + RH \rightarrow H_2 + R'$$
$$CH_3' + RH \rightarrow CH_4 + R'$$

for which some experimental data are available.

As standard entropies of hydrocarbons and of the hydrogen atom (S^0) at one

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atmosphere pressure are available from tables (13), the problem resolves itself into calculating S^0 values for the CH_3' radical and the intermediate complexes by estimating bond distances and bond angles and thus calculating translational, rotational, vibrational, and electronic contributions to the total entropy. The appropriate formulae for the "harmonic oscillator – rigid rotator" approximation are conveniently collected in a review by Wilson (16) or can be found in textbooks of statistical thermodynamics. Throughout, the calculations are made in "virtual" entropy units (i.e., neglecting nuclear spin contributions since they do not change in reactions) and originally refer to unit pressure and are converted to a unit concentration basis in the final stage.

ENTROPY OF THE METHYL RADICAL

No spectroscopic data on the configuration of this radical are yet available, however, evidence for the planarity of the radical has been presented by Walsh (14) and by Waters (15) and so a planar configuration has been assumed. The symmetry number is therefore six. The C-H bond distance has been assigned a value of 1.11Å although Walsh suggests that it should be slightly larger. The error involved will however be small. The electronic state is $^2A_1$ according to Mulliken (8) and therefore a contribution R ln 2 has been included as electronic entropy. Calculated total entropy values are given in Table I. The values given there differ slightly from those estimated by Zeise (17), the difference being almost entirely due to his choice of a pyramidal structure with consequent reduction of the symmetry number from six to three.

TABLE I

STANDARD ENTROPY OF THE METHYL RADICAL (S^0) AT ONE ATMOSPHERE

T,°K.	300°	400°	500°	600°	700°
S^0	46.1	48.6	50.7	52.2	54.2

ENTROPY OF INTERMEDIATE COMPLEXES

Model complexes have been used throughout in which normal tetrahedral angles have been assumed. All C-H and C-C bond distances have been estimated as 1.11Å and 1.53Å respectively except for the two C-H bonds linking the two molecular halves of the complex which have been assigned a length of 1.28Å, in accordance with the cases worked out by Eyring and co-workers where from potential energy surfaces it was shown that these two bonds are lengthened. Exceptions to these general rules were made in the case of the H_3^* complex where Eyring's theoretically calculated bond lengths were used, and in the case of $C_2H_7^*$ and $C_4H_{11}^*$ where the extra hydrogen atom will only make a very small change in the moment of inertia and so the values given by Kassel (5) for C_2H_6 and C_4H_{10} respectively have been used, together with the appropriate change in symmetry number. Moments of inertia calculated by this means are given in Table II.

Vibrational assignments have been made according to the principles laid out

TABLE II

CALCULATED MOMENTS OF INERTIA $\times 10^{40}$ GM. CM.^{2}

Compound	I_a	I_b	I_c
CH_3	6.1	3.05	3.05
$H—CH_4$	15.7	15.7	5.46
$CH_3—CH_4$	92.3	92.3	11.0
$CH_3—C_2H_6$	184.2	152.4	31.8
$CH_3—HC:(CH_3)_3$	274.0	274.0	178.0

by Pitzer (9) for saturated hydrocarbons. Since the vibrational contribution is small, little error should result.

It has been assumed that where the possibility of internal rotation of methyl groups occurs, the methyl groups have the same hindering potential as in the parent hydrocarbon. Hindering potentials as given by Pitzer (9) have been used for this purpose together with tables (10) given by him for the loss of entropy at various temperatures. Rotation of the attacking methyl group has been assumed to be unhindered since it is further away from other methyl groups than in existing molecules, and presumably therefore interaction is weaker.

An electronic contribution of R ln 2 has been included since the complex still possesses an unpaired electron and presumably no change in electronic configuration occurs between reactants and the complex.

The translational entropy can be calculated accurately from the molecular weight. It makes by far the largest contribution to the total entropy.

All calculations were carried out at 100° temperature intervals between 300° K. and 700° K. to check on the constancy of the final temperature independent factor. In all cases "A" was found to be temperature independent. The calculation of the entropy of a typical complex C_2H_7* is given in Table III as an example of the methods used.

TABLE III

CALCULATION OF THE STANDARD ENTROPY (S^0) OF THE C_2H_7* COMPLEX AND THE A-FACTOR FOR THE REACTION $H + C_2H_6$

T, °K.	300°	400°	500°	600°	700°
Strans. & rot.	56.2	58.5	60.3	61.7	63.0
Svibration	0.7	1.9	3.6	5.5	7.5
Sint. rot.	1.8	2.3	2.8	3.2	3.5
Selectronic	1.4	1.4	1.4	1.4	1.4
Stotal	60.1	64.1	68.1	71.8	75.4
$-\Delta S_p$*	22.3	23.7	24.7	25.6	26.3
"A" ($\times 10^{-13}$)	1.5	1.3	1.2	1.2	1.2

The final results of the calculations are given in Table IV with the corresponding experimental values. The latter have been taken from Steacie and Szwarc (11), from Berlie and Leroy (1), and from Majury and Steacie (7). Transmission coefficients (κ) have been assumed to be unity throughout. The investigations of Gomer and Kistiakowsky (4) and Lucas and Rice (6) on the

TABLE IV

PRE-EXPONENTIAL FACTORS FOR HYDROGEN ABSTRACTION REACTIONS (CC. MOLE^{-1} SEC.$^{-1}$) THEORETICAL AND EXPERIMENTAL VALUES

Attacking radical	Pre-exponential factor							
	H_2		CH_4		C_2H_6		iso-C_4H_{10}	
	Calc.	Obs.	Calc.	Obs.	Calc.	Obs.	Calc.	Obs.
H	5×10^{13}	3.5×10^{13}	2×10^{13}	—	1.2×10^{13}	$\begin{cases}3\times10^{14}\\1\times10^{12}\end{cases}$	4×10^{12}	—
CH_3	1×10^{12}	2×10^{12}	8×10^{10}	—	9×10^{10}	2×10^{11}	6×10^{9}	1×10^{11}

recombination of methyl radicals show that κ must be near unity for this reaction. It seems likely that in hydrogen abstraction reactions, κ should not have a lower value since there is a much smaller amount of excess energy in the complex, decreasing its tendency to dissociate.

DISCUSSION

It is interesting to consider the possible sources of error in this type of calculation bearing in mind that pre-exponential factors vary over several powers of 10 in various reactions and experimental values accurate to a factor of two or three must be considered very satisfactory. The errors will be concentrated in the estimation of rotational and vibrational entropies. It should be noted that an error of two entropy units produces about a factor of two in the final pre-exponential factor.

Considering the rotational entropy, such an error is produced only if all three principal moments of inertia are incorrect by a factor of two. Even using approximate bond lengths and angles it should be virtually impossible to make such an error. Internal rotation of methyl groups poses the most difficult question particularly in the ethane or isobutane case. It appears however very reasonable that, for example, the three methyl groups in the isobutane complex should have the same hindering potential as in isobutane since they are relatively remote from the seat of reaction. Using this assumption the uncertainty is narrowed down to the rotational entropy of the attacking methyl group. Here the difference between free rotation and hindered rotation with a barrier of around 3000 cal. per mole is 1.4 e.u. at 300° K. and is naturally lower at higher temperatures.

The total vibrational entropy in the complex is 4 e.u. at 300° K. as a maximum (Table III). Considerable inaccuracies in vibrational assignments can therefore be made without making a serious error in the total entropy.

The Hydrogen Atom Series

The largest entropy change in complex formation is the loss of the translational entropy of the hydrogen atom (Table VI). From ethane onwards this is entirely lost (26.0 e.u.) since the translational entropy of the complex is identical (within the limits of accuracy of calculation of 0.1 e.u.) to that of the hydrocarbon (Table V). This is balanced by a gain in rotational entropy (6.5 e.u. for H_2,

TABLE V

TRANSLATIONAL AND ROTATIONAL ENTROPIES AT 300°K. AND ONE ATMOSPHERE

Hydrocarbon	H_2	CH_4	C_2H_6	iso-C_4H_{10}
$S^0_{trans.}$ (RH)	28.2	34.3	36.1	38.1
$S^0_{trans.}$ (H–RH)	29.3	34.4	36.2	38.2
$S^0_{trans.}$ (CH_3–RH)	34.4	36.2	37.4	38.8
$S^0_{rot.}$ (RH)	2.1	10.0	16.4	22.4
$S^0_{rot.}$ (H–RH)	8.6	15.1	19.9	22.3
$S^0_{rot.}$ (CH_3–RH)	15.1	18.0	23.7	24.3

2.25 for CH_4) which rapidly disappears as the complexity of the molecule increases. That is, the rotational entropy of the complex becomes equal to that of the hydrocarbon attacked if the symmetry contribution is omitted. No change occurs in vibrational and electronic contributions. Isobutane has reached what should be the lowest A-factor, corresponding to $\Delta S_p^* = -26.0$ e.u. Higher hydrocarbons should have A-factors between 4×10^{12} and 2×10^{13} decided entirely by the various changes in symmetry number on forming the complex. Thus highly symmetrical hydrocarbons such as neopentane should have the higher values in the range. It must be noted that all reaction with isobutane has been assumed to occur at the tertiary hydrogen atom since this reaction shows a considerably lower activation energy (12).

Methyl Radical Reactions

The same principles apply in this series except that since the methyl radical is more massive than the hydrogen atom the limiting value of ΔS_p^* occurs with higher hydrocarbons only. The loss of translational entropy on complex formation reaches a limiting value of 34 e.u. (the translational entropy of CH_3) at about the pentanes (see Table VI). In the lower hydrocarbons there is a gain of

TABLE VI

CHANGES IN ENTROPY ON COMPLEX FORMATION (300°K. AND ONE ATMOSPHERE)

Attacking radical	Hydrocarbon	H_2	CH_4	C_2H_6	iso-C_4H_{10}
H	$\Delta S_{translation}$	− 25.1	− 25.9	− 26.0	− 26.0
	$\Delta S_{external\ rotation}$	+ 5.1	+ 2.3	− 0.1	0.0
	$\Delta S_{internal\ rotation}$	0.0	0.0	+ 0.1	+ 0.3
CH_3	$\Delta S_{translation}$	− 27.9	− 32.2	− 33.0	− 33.4
	$\Delta S_{external\ rotation}$	+ 3.1	− 4.1	− 7.0	− 8.8
	$\Delta S_{internal\ rotation}$	0.0	+ 3.0	+ 4.0	+ 4.0

Note: *Symmetry contribution omitted from* $\Delta S_{external\ rotation}$.

external rotational entropy due to increased moment of inertia in the complex. This gradually decreases to zero, until the only gain is around 4 e.u. of internal rotation of the attacking methyl group, replacing its 10.7 rotational entropy units in the free state. Thus in the pentanes and higher hydrocarbons the maximum change in ΔS_p^* is around -40 e.u. producing the lowest possible A-factor. Variations between this minimum (6×10^9) and values approximately a power

of 10 higher should again be decided only by symmetry relations in the higher hydrocarbons, highly symmetrical hydrocarbons having the highest A-factors. The calculated value for the isobutane reaction should again be considered an absolute minimum value since only reaction with the tertiary hydrogen atom has been considered.

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MOLTEN SALTS. ELECTRICAL TRANSPORT IN THE SYSTEM SILVER NITRATE – SODIUM NITRATE[1]

By P. M. Aziz and F. E. W. Wetmore

ABSTRACT

Relative transport fractions have been measured in the molten system silver nitrate – sodium nitrate at 330° over the range 5 to 25 mole% silver nitrate. The individual fractions for silver, sodium, and nitrate ion have been assessed within limits. The results indicate that transport by silver ion is greater than that by sodium ion at the same concentration, although the latter has the smaller radius. The usual assumption that the largest ion (nitrate) does not transport charge is within the interpretation of the results.

INTRODUCTION

The determination of transport numbers in molten salt systems presents a situation not encountered in aqueous solutions. In binary solutions of the latter type only two conducting species need be considered, since a correction can be applied for the contribution of the solvent, and a Hittorf transport number for each species can be determined from concentration change during electrolysis. The binary molten system silver nitrate – sodium nitrate, on the other hand, has at least three possible conducting species and there is no indifferent solvent to act as a frame of reference for changes in concentration. Any change in the proportion of silver nitrate demands a change in the proportion of sodium nitrate. A single concentration change cannot yield three transport numbers and only relative values can thus be obtained.

In order to avoid any ambiguity about defining transport numbers for salt melts, the "transport fractions" θ_1, θ_2, θ_3 will be used to designate the number of equivalents of silver, sodium, and nitrate ion, respectively, transported per Faraday of charge passed through a melt.

Let z Faradays of charge be passed through a melt having the initial composition expressed in equivalent fractions (here mole fractions): N_1^0 of silver nitrate and N_2^0 of sodium nitrate. Electrolysis of the melt between silver electrodes will result in the anolyte gaining $z(1 - \theta_1)$ equivalents of silver nitrate and $-z\theta_2$ equivalents of sodium nitrate. The anolyte sample is here defined as an indefinite portion of the electrolyte about the anode which meets the condition that it include all variations from the initial composition. Analysis of the anolyte sample taken after electrolysis shows that it consists of n_1 equivalents of silver nitrate and n_2 of sodium nitrate, and has the corresponding concentration $N_1 = n_1/(n_1 + n_2)$ of silver nitrate. The anolyte sample may be considered as consisting of a portion of melt of the initial composition, containing n_1^0 equivalents of silver nitrate and n_2^0 of sodium nitrate, along with the modifications due to electrolysis, so that

$$n_1 = n_1^0 + z(1 - \theta_1) \tag{1}$$

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Contribution from the Electrochemical Laboratory, University of Toronto, Toronto 5, Canada.

$$n_2 = n_2^0 - z\theta_2. \tag{2}$$

Further, $$n_2^0 = n_1^0 N_2^0 / N_1^0 \tag{3}$$

and $$\theta_1 + \theta_2 + \theta_3 = 1 \text{ (for electrolytic conduction).} \tag{4}$$

From the above four relations,

$$1 - \theta_1 - N_1^0\theta_3 = \theta_2 + N_2^0\theta_3 = (n_1 + n_2)(N_1 - N_1^0)/z = \phi. \tag{5}$$

Equation 5 shows that the transport fractions can be related to experimentally determinable quantities, but cannot be determined separately from changes in concentration. However, it will be shown in the discussion of results that the possible values for silver are confined to fairly narrow limits.

EXPERIMENTAL PROCEDURES

The salts used were thrice recrystallized from aqueous solution without change in the conductivity of the pure melt. The silver nitrate content of the binary melts was determined gravimetrically by precipitation of silver chloride.

Schwartz (4) used vertical cells in an attempt to measure transport numbers in melts, but found, as might be expected, that transport by convection was very great. The cells used here were of Pyrex glass in an H-form, with an extended and folded horizontal tube (about 1.8 mm. internal diameter) between the anode and cathode limbs. Small bulbs were blown in the connecting tube near the anode limb; the contents of these bulbs were analyzed to show how far along the tube variation of composition occurred during electrolysis.

Electrodes of heavy silver wire, 99.99% pure, were used. In early runs it was found that treeing of the cathode deposit quickly caused a short-circuit in the cell. The cathode was therefore rotated to break off the filaments of deposited silver within the cathode limb. The furnace consisted of a copper slug, housing the anode end of the cell, set in a steel box wound with a Nichrome heating element. The box was immersed in sand within a thermally lagged container. The runs were carried out at approximately 330°.

The electrolyzing current, approximately 60 ma. for most runs, was supplied from a power pack of constant output voltage; a large variable resistor served for controlling the current.

The usual Hittorf criterion was applied for each run. After electrolysis the whole cell was chilled with an air blast and a sample of some 10 gm. taken by cutting off the limb containing the anode. Two smaller samples of about a gram weight were taken by cutting off the small bulbs. If the variation of composition from the original value in the last two samples was small enough to be not contributory (less than 1% of the total variation), the run was accepted. On this basis of acceptance about two-thirds of the runs were rejected; only two acceptable results were obtained at $N_1^0 = 0.24$ and therefore no measurements were attempted with melts having a higher proportion of silver nitrate. Table I gives the significant details of the acceptable runs.

TABLE I

RESULTS OF TRANSPORT DETERMINATIONS

N_1^0	n_1	n_2	n_1+n_2	N_1	$N_1-N_1^0$	z	ϕ
0.05069	0.006043	0.10766	0.11371	0.05315	0.00246	0.000344	0.813
	.005993	.10406	.11005	.05446	.00377	.000523	.793
	.005940	.10242	.10836	.05482	.00413	.000555	.806
	.005813	.09811	.10392	.05593	.00525	.000672	.812
							Av. 0.806
0.11552	0.009565	0.06642	0.07598	0.12589	0.01037	0.00124	0.635
	.012662	.09052	.10318	.12272	.00720	.00112	.663
	.012929	.09379	.10672	.12115	.00563	.00112	.536
	.011238	.08186	.09310	.12071	.00519	.000859	.562
							Av. 0.60
0.17918	0.015907	0.07190	0.08781	0.18115	0.00197	0.000560	0.309
	.018036	.08200	.10004	.18030	.00112	.000373	.300
	.016846	.07648	.09332	.18052	.00134	.000373	.335
							Av. 0.315
0.24353	0.028581	0.08847	0.11705	0.24419	0.00066	0.000597	0.129
	.024214	.07473	.09894	.24473	.00120	.000746	.159
							Av. 0.144

DISCUSSION OF RESULTS

It has been common practice to assume that ions of large "radius" have smaller mobilities than those of small "radius" (2, 3). The assumption here would be that nitrate ion does not conduct charge and that sodium ion conducts more charge than silver ion in proportion to their relative concentrations. No such assumption will be made here; instead, the experimental results will be examined to find whether an answer is provided.

In all determinations of transport numbers it is customary to assume a set of simple ionic constituents and to assess their transport fractions by determining their ratios of mass movement. If any of the ratios turn out to be negative, it is usual to select a new set of ionic constituents, this time including complex ions, and to recalculate transport numbers. Ultimately there can be found a set which will yield positive transport numbers. Here the same process will be followed. It will therefore be assumed that the quantities θ_1, θ_2, and θ_3 all lie within the range zero to unity.

From equation 5, $\theta_1 = 1 - \phi - N_1^0\theta_3$. The upper limit for the value of θ_1 is obtained by setting $\theta_3 = 0$. For $N_1^0 = 0.051$, $\theta_1^{max} = 0.194$. The lower limit for θ_1 can be obtained by successive approximations of the value of θ_3, beginning with unity. The first approximation gives $\theta_1 \geqslant (0.194 - 0.051) = 0.143$. From this, $\theta_3 \leqslant (1 - 0.143) = 0.857$. Finally, $\theta_1^{min} = 0.150$. From the data of Table I the upper and lower limits of the vertical lines of Fig. 1 were thus obtained.

It seems unreasonable to assume that θ_1 should increase up to $N_1^0 = 0.24$ and then become constant or diminish with increase in the proportion of silver nitrate in the melt. Therefore it is inferred that θ_3 in pure silver nitrate must be very

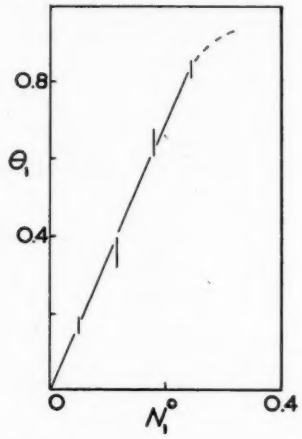

Fig. 1. Transport fraction for silver in silver nitrate – sodium nitrate melts at 330°.

small or even zero. The experimental results presented here do not permit assessment of θ_2, but do show the limits of $(\theta_2 + \theta_3) = 1 - \theta_1$.

It is apparent that silver ion conducts more charge than sodium ion in proportion to their relative concentrations. This finding is in agreement with the conductivity data for this system (1, 5), which show that silver nitrate has a slightly higher equivalent conductivity than sodium nitrate at 330°, and that the energy of activation for mobility of silver nitrate (2690 cal. mole^{-1}) is lower than that for sodium nitrate (3270 cal. mole^{-1}). There is no evidence which negates the assumption that nitrate ion has a low mobility in sodium nitrate, and hence in the binary melts.

ACKNOWLEDGMENTS

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THE CHARACTERIZATION OF NARCOTICS AS REINECKATES[1]

By Leo Levi[2] and Charles G. Farmilo[2]

ABSTRACT

Ammonium reineckate was found to react with methorphinan hydrobromide, codeine phosphate, and the hydrochlorides of methadone, phenadoxone, pipidone, cocaine, pethidine, ketobemidone, alphaprodine, morphine, diamorphine, and metopon to yield characteristic crystals. The molecular composition, decomposition range, optical rotation, solubility in water and ethanol, and spectral transmittance of these crystalline compounds are reported with the pK_B values of the narcotics in water and in 50% acetone.

INTRODUCTION

The metathetical reaction occurring in aqueous solution between amine salts and ammonium reineckate (Reinecke salt) in accordance with the equation

$$RN \cdot HX + NH_4 \cdot [Cr(NH_3)_2 \cdot (SCN)_4] \rightleftharpoons NH_4X + RN \cdot H \cdot [Cr(NH_3)_2 \cdot (SNC)_4]$$

has often been used as a method of isolation, characterization, and quantitative estimation of nitrogenous bases. Christensen (6) first made a thorough study of the reaction in 1892 and synthesized reineckates of both simple amines and alkaloids. He also included morphine and cocaine in his investigations but did not subject the reineckates to further physicochemical characterization. Thirty-five years later Rosenthaler (21) observed that the derivatives obtained by the interaction of Reinecke salt and a number of alkaloids were crystalline compounds whose habits could be recognized and studied under the microscope. He did not subject the reaction products to physical or chemical analysis but gave a series of line drawings to illustrate their characteristic features and suggested that Reinecke salt be used as a general alkaloidal precipitant. Soon after its introduction in alkaloid chemistry the reagent was utilized by biochemists for the isolation and identification of amino acids found in biological materials (15, 16, 17, 23, 25). Coupechoux (8) in 1939 prepared 36 crystalline reineckates including simple amines, amino acids, and heterocyclic nitrogenous bases and determined their composition and solubility. He also observed that narcotics, e.g., morphine, codeine, dionin, and diamorphine, gave precipitates with ammonium reineckate. However, these salts were not analyzed and none of their physical constants reported. Aycock, Eisenbraun, and Schrader (1) who synthesized some of the reineckates which were prepared by Christensen and Coupechoux observed that these compounds possessed sharp melting points. Recently Wilson (27) reported that quaternary ammonium bases used as antiseptics, disinfectants, and detergents in the food industry also yield crystalline reineckates whose optical properties are highly characteristic and may serve to identify these substances. Evans and Partridge (10) used ammonium reineckate for the characterization of two solanaceous alkaloids (hyoscine and hyoscyamine) obtained by partition chromatography from *Atropa belladonna* and *Datura*

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stramonium and Fried and Wintersteiner (12) were able to separate two high molecular weight water-soluble bases (streptomycin and streptothricin) from submerged-culture filtrates of the respective *Actinomyces* in the form of crystalline reineckates. In general, these derivatives are quite insoluble in water and because they have a relatively high molecular weight a number of workers have utilized their formation for the quantitative determination of small amounts of many organic bases (2, 3, 4, 5, 9, 10, 19, 20, 24, 26). As a result of these investigations ammonium reineckate has become one of the most versatile reagents for the identification and estimation of amines. However, it has not yet been utilized systematically to characterize narcotic drugs and it is the object of the present investigation to evaluate its potentialities in this field.

EXPERIMENTAL

Materials

The narcotics investigated in this study were obtained from the following sources of supply: Physeptone[R*], brand of amidone hydrochloride,—Burroughs Wellcome and Co., London, England; Heptalgin[R], brand of phenadoxone hydrochloride,—Glaxo Laboratories Ltd., Greenford, Middlesex, England; pipidone hydrochloride,—Burroughs Wellcome and Co., England; Demerol[R], brand of meperidine hydrochloride,—Winthrop-Stearns, Inc., Windsor, Ont.; Cliradon[R], brand of ketobemidone hydrochloride,—Ciba Ltd., Basle, Switzerland; Nisentil[R], brand of alphaprodine hydrochloride,—Hoffmann-LaRoche Inc., Nutley, N.J.; cocaine hydrochloride,—Burroughs Wellcome and Co., London, England; Dromoran[R], brand of methorphinan (*dl*)hydrobromide,—Hoffmann-LaRoche Inc., Nutley, N.J.; Heroin[R] hydrochloride,—T. and H. Smith Ltd., Edinburgh, Scotland; codeine phosphate,—May and Baker Ltd., Montreal, Canada; morphine hydrochloride,—T. and H. Smith Ltd., Edinburgh, Scotland; metopon hydrochloride,—Parke Davis and Co., Walkerville, Ont.

The ammonium reineckate used was reagent grade material, supplied by British Drug Houses (Canada) Ltd.

Procedures

Excess aqueous ammonium reineckate (3%) was added slowly and with constant stirring to the slightly acidified aqueous solution (1%) of the narcotic. After refrigerating the reaction mixture for eight hours at 5° C. the narcotic reineckate was filtered off and dried *in vacuo* over phosphorus pentoxide. Product yields exceeded 80% of the theoretical in all experiments. Purification of the reineckates was accomplished by warming in 50% ethanol at 60° C. (higher temperature caused decomposition), filtering, and refrigerating. Two or three recrystallizations yielded compounds sufficiently pure for physicochemical characterization. Melting points (corrected) were taken on a Fisher-Johns melting point apparatus using a heating rate of 5° C. per minute. Chromium analyses were carried out by ignition of about 0.1 gm. samples to constant weight (Cr_2O_3). Optical rotations (ethanol 95%; $c = 0.1$) were measured on a Hilger polarimeter and spectral transmittances in acetone were determined on

**The symbol [R] denotes a registered trade-mark. Nonproprietary or official names are used throughout the body of the text.*

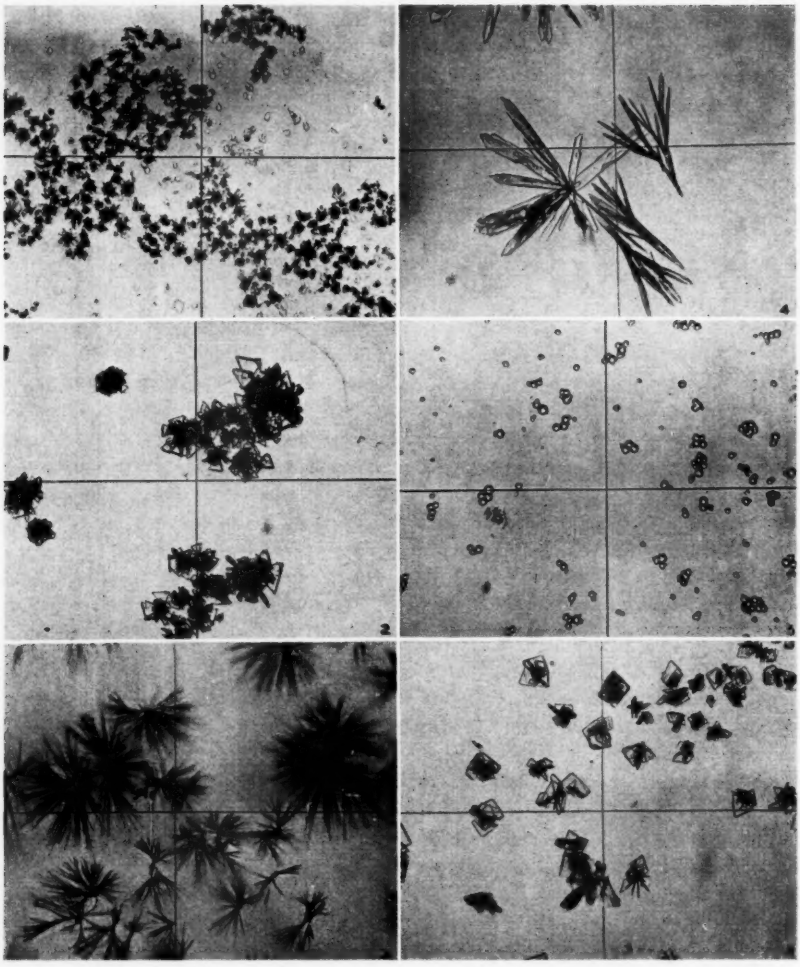
0.004 molar solutions using a Beckman Model B spectrophotometer. The pK values of the narcotic bases in water and 50% aqueous acetone were obtained in accordance with the method given by Saunders (22) and solubility determinations in 95% ethanol and water were made at 23.5° C. following the procedure adopted by Coupechoux (8).

The crystalline products were prepared for photomicrography by placing one drop (approximately 0.03 cc.) of an aqueous–alcoholic solution (1:1) containing 10 mgm. of the purified reineckate per cubic centimeter on a microscope slide and allowing spontaneous evaporation to proceed at room temperature (25° C.) until crystal growth could be observed. In no instances were the slides scratched to hasten the crystallization process and the use of cover glasses was avoided since they tended to cause formation of distorted crystals. The photographic apparatus comprised a Bausch and Lomb Model L. camera and a Spencer microscope set up for 10× objective with Kohler critical illumination for low magnification. The ocular was a 10× normal Spencer, with a 10× objective and a 17½ in. bellows extension. All crystals were photographed without filters using a zircon arc microscope lamp. Light readings as measured on the ground glass by a Photo-volt, Model 200, sensitive light meter were about 12.5 units on the high scale. The exposure time was found to be about 1/50 sec. under these conditions. The photos were taken on 5 in. × 7 in. super XX panchromatic film developed in a modified D-76 developer for seven minutes. The total enlargement is 140 times.

DISCUSSION

It was found that formation of the derivatives occurred readily on addition of the ammonium reineckate reagent to the aqueous solution of the narcotic which had been acidified with dilute hydrochloric acid to a pH of about 4.0–4.5 in order to secure maximum product yields (9). By carrying out the addition slowly, with gentle stirring, large crystals or coarse amorphous precipitates that were easy to filter could be obtained. Of the narcotics investigated morphine, methorphinan, and ketobemidone were found to give directly distinctive microcrystalline precipitates whereas all other narcotic-reineckates required purification in order to obtain characteristic crystal formations. The identification of morphine by means of Reinecke salt is well known to the forensic chemist but the use of this reagent for the microchemical identification of both methorphinan and ketobemidone has not yet been reported in the literature as far as we could determine. Conditions for optimum crystal growth with regard to concentration of the narcotic and sensitivity of the reagent are reported elsewhere (11). The photomicrographs shown in Figs. 1–12 clearly illustrate that even structurally closely related narcotics yield with Reinecke salt crystals of distinctly different habits which emphasizes the value of this precipitant as a specific microchemical reagent for the analysis of narcotics.

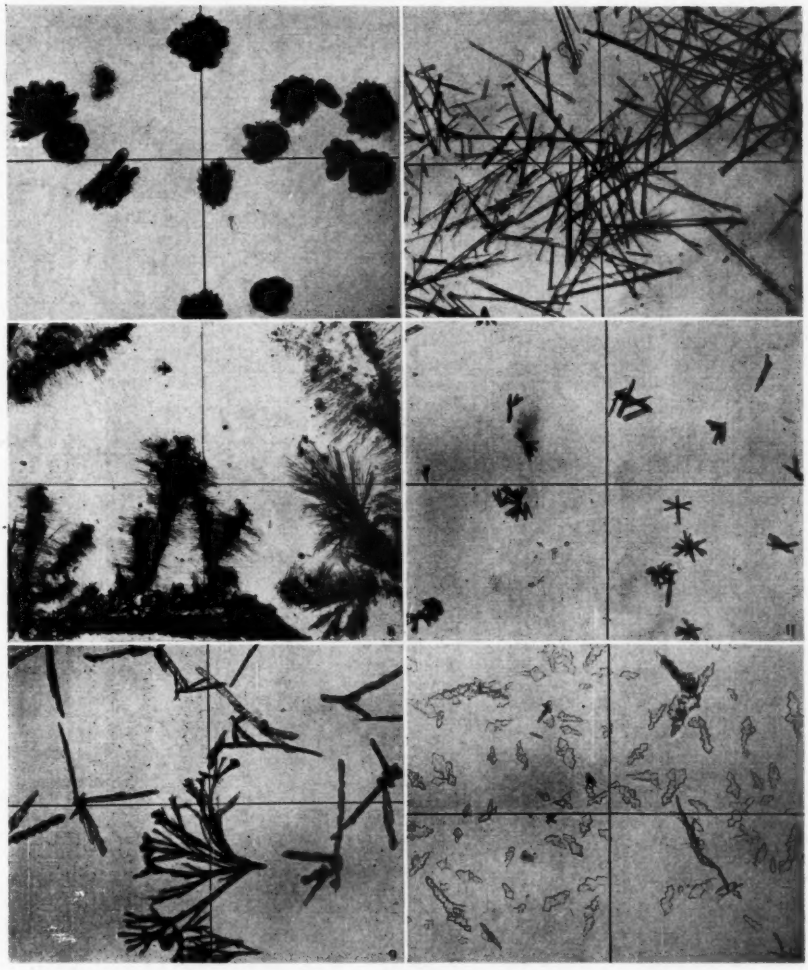
All of the narcotic-reineckates prepared were found to be anhydrous quaternary ammonium compounds. After they had been dried *in vacuo* over phosphorus pentoxide they could be heated to 100° C. for about one hour without suffering loss of weight. They were found to decompose over a narrow temperature range.



Figs. 1 – 6. Crystals of narcotic-reineckates.

Fig. 1. Cocaine reineckate.
Fig. 2. Codeine reineckate.
Fig. 3. Pethidine reineckate.
Fig. 4. Dromoran reineckate.
Fig. 5. Diamorphine reineckate.
Fig. 6. Ketobemidone reineckate.

In most instances a momentary melting to a clear red liquid just prior to decomposition was noted. Only morphine, diamorphine, and metopon showed a rather gradual decomposition without accompanying liquefaction. The alkanoneamines melted at about 160° C., the arylpiperidines from 135–175° C., and the hydrophenanthrenes from 165–255° C. In all cases the melting points of the reineckates were lower than those of the narcotics from which they had been prepared (Table I). The depression amounted to about 30–70° C.



Figs. 7 – 12. Crystals of narcotic-reineckates.

Fig. 7. Metopon reineckate.
Fig. 8. Morphine reineckate.
Fig. 9. Nisentil reineckate.
Fig. 10. Phenadoxone reineckate.
Fig. 11. Pipidone reineckate.
Fig. 12. Methadone reineckate.

Although the narcotic-reineckates were thus found to be stable compounds in the dry state it was observed that their aqueous as well as alcoholic solutions were unstable. On standing for two to three days at room temperature formation of a precipitate and loss of color was noticed. The compounds were all fairly soluble in 95% ethanol but only slightly soluble in water. The alkanoneamines, in particular, yielded reineckates which were practically water-insoluble. This finding strongly suggests that these narcotics may be quantitatively determined

TABLE I

PHYSICOCHEMICAL CHARACTERIZATION OF NARCOTIC-REINECKATES

Narcotic	Molecular composition of narcotic-reineckate	Cr., %		Decomposition range, °C.		Optical rotation $[\alpha]_D^{24.8}$	Solubility, % w/v		1 gm.mol./l. E 1 cm.		pK*A* value of narcotic base as determined on:		Difference
		Calc.	Found	Narcotic-reineckate	Narcotic		Water	Ethanol 95%	525 mμ	395 mμ	Narcotic-reineckate in 50% aq. acetone	Narcotic-halide in water	
A. Alkanoneamines													
Methadone hydrochloride[1]	$C_{25}H_{34}N_7CrS_4O$	8.27	8.36	160-164	232-235	0	0.002	0.519	106.7	86.6	8.9	Precipitated	—
Phenadoxone hydrochloride[2]	$C_{27}H_{36}N_7CrS_4O_2$	7.75	7.79	162-165	220-230	0	0.008	0.256	107.1	85.9	6.7	Precipitated	—
Pipidone hydrochloride[3]	$C_{28}H_{33}N_7CrS_4O$	7.78	7.82	164-166	189-196	0	0.005	0.414	106.2	87.1	8.3	Precipitated	—
B. Arylpiperidines													
Pethidine hydrochloride[4]	$C_{19}H_{28}N_7CrS_4O_2$	9.18	9.26	136-138	185-188	0	0.004	1.717	106.3	85.6	7.9	8.6	0.7
Cocaine hydrochloride	$C_{31}H_{38}N_7CrS_4O_4$	8.35	8.39	159-162	195-197	−56°	0.011	0.351	106.8	86.5	8.0	8.6	0.6
Alphaprodine hydrochloride[5]	$C_{20}H_{30}N_7CrS_4O_2$	8.96	9.01	172-174	223-229	0	0.007	0.278	107.4	87.0	7.9	8.6	0.7
Ketobemidone hydrochloride[6]	$C_{19}H_{28}N_7CrS_4O_2$	9.18	9.12	173-176	196-199	0	0.033	1.132	106.1	85.8	8.0	8.5	0.5
C. Hydrophenanthrenes													
Methorphinan(*dl*)hydrobromide[7]	$C_{21}H_{30}N_7CrS_4O$	9.02	8.97	165-167	194-196	0	0.019	1.079	107.3	86.9	8.8	Precipitated	—
Diamorphine hydrochloride[8]	$C_{25}H_{30}N_7CrS_4O_5$	7.55	7.58	180-185	228-232	−74°	0.042	1.528	105.7	85.6	7.3	7.8	0.5
Codeine phosphate	$C_{23}H_{32}N_7CrS_4O_3$	8.40	8.47	189-193	233-237	−57°	0.068	0.927	106.4	86.3	7.6	8.1	0.5
Morphine hydrochloride	$C_{21}H_{28}N_7CrS_4O_3$	8.61	8.65	204-209	250-260	−62°	0.039	0.372	105.9	85.8	7.6	8.1	0.5
Metopon hydrochloride[9]	$C_{22}H_{28}N_7CrS_4O_3$	8.40	8.32	246-253	314-318	−65°	0.047	0.337	106.9	86.0	7.6	8.1	0.5

1 *Methadone;* (*amidone, Physeptone*^{R}) dl-*6-dimethylamino-4,4-diphenylheptanone-3.*
2 *Phenadoxone;* (*Heptalgin*^{R}) dl-*6-morpholinyl-4,4-diphenylheptanone-3.*
3 *Pipidone;* dl-*6-piperidyl-4,4-diphenyl-5-methylhexanone-3.*
4 *Pethidine;* (*Demerol*^{R}, *meperidine*) *ethyl 1-methyl-4-phenylpiperidine-4-carboxylate.*
5 *Alphaprodine;* (*Nisentil*^{R}) dl-α-*1,3-dimethyl-4-phenyl-4-propionoxypiperidine.*
6 *Ketobemidone;* (*Cliradon*^{R}) *1-methyl-4-*(m-*hydroxyphenyl*)-*piperidylethyl ketone.*
7 *Methorphinan;* (*Dromoran*^{R}) dl-*3-hydroxy-N-methyl morphinan.*
8 *Diamorphine;* (*Heroin*^{R}, *diacetylmorphine*).
9 *Metopon; methyldihydromorphinone.*
(*Small, L. and Sargent, L. J. Science, 112:473. 1950.*)

by precipitation with ammonium reineckate. Such analyses have been carried out by Duquénois (9) on cocaine, narcotine, papaverine, and morphine. Bandelin (2) however found that morphine was not quantitatively precipitated by Reinecke salt and his finding appears to be supported by our observation that morphine reineckate is soluble in water to the extent of 0.039% (Table I).

Rotations of the optically active narcotic-reineckates were found to be lower than those of the free bases with the exception of the cocaine derivative. Concentrations higher than 0.1% could not be used for these measurements because the compounds imparted a pale rose color to their solutions.

The extinction coefficients were determined according to standard procedure. Using 0.004 molar solutions of the narcotic-reineckates the same transmittance–wave length curve (maxima at 395 and 525 mμ respectively) was always obtained (see Fig. 13) and pure ammonium reineckate was found to show identical

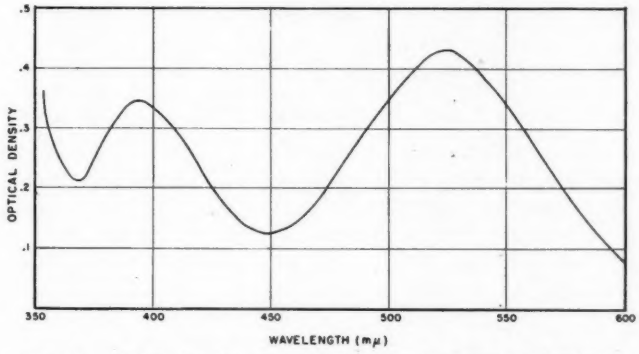


Fig. 13. Optical density – wave length curve for narcotic-reineckates.

absorption. Hence, the intensity of the color developed by narcotic–reineckates in acetone solutions is independent of the nature of the conjugate base and determined by the reineckate group exclusively. A similar phenomenon was observed by Örtenblad (19) during a study of the reineckate method for the quantitative determination of xylocaine in mixtures of xylocaine and procaine hydrochloride.

The crystalline derivatives were used to measure the pK_A values of the base components by potentiometric analysis. Most of the narcotic-reineckates were not sufficiently water-soluble to carry out the determinations in pure aqueous solutions and all titrations were, therefore, performed in a 50% aqueous solvent system. The experimental data, approximated to one place decimals without consideration of the difference between thermodynamic and stoichiometric constants, were all lower than those obtained on the corresponding narcotic-halides in water (Table I). This finding is in agreement with Saunders' observation that the acid dissociation constant exponents (pK_A) of the alkaloids decrease as the nonaqueous component of the solvent system is increased (22). The pK_A value of ammonium reineckate was found to be 8.7 when determined

in a 50% aqueous acetone solution as compared to 9.3 when determined in water, and a pK_A depression of this order of magnitude was found for all of the narcotics with regard to these two solvent systems. Methorphinan and all the alkanoneamines were precipitated on addition of alkali to their aqueous halide solutions and no pK_A values were established for these compounds in water. Their marked water-insolubility was found to be retained by the corresponding reineckates. The alkanoneamine-derivatives were only slightly water-soluble compounds and methorphinan-reineckate was found to be the least water-soluble member of the hydrophenanthrene class. On the other hand some of the reineckates, e.g., those of alphaprodine and cocaine, which were found to be but slightly soluble in water were derived from bases more water-soluble than methorphinan or any of the alkanoneamines (Table I).

From the experimentally determined pK_A values the basic dissociation constant exponents pK_B of the narcotics were calculated using the relationship $pK_B = pK_W - pK_A$. The value of pK_W for pure water is approximately 14.2 at 20° C. but in mixed solvents such as aqueous acetone the value of pK_W will be slightly higher (13). Assuming that the organic solvent acts only by diluting the water and that the dissociation constant of water $\frac{[H^+] \cdot [OH^-]}{[H_2O]}$ remains unchanged the pK_W for 50% aqueous acetone is about 14.5. Using these data and relationships for calculating pK_B values the narcotics investigated could be arranged according to their degree of basicity in both 50% aqueous acetone and pure water (Table II).

TABLE II

pK_B VALUES OF NARCOTICS IN 50% AQUEOUS ACETONE AND WATER

Narcotic	pK_B value of narcotic		
	50% Aqueous acetone	Water	
Phenadoxone	7.8	—	
Diamorphine	7.2	6.4	6.4*
Codeine	6.9	6.1	6.05**
Morphine	6.9	6.1	6.13**
Metopon	6.9	6.1	
Pethidine	6.6	5.6	
Alphaprodine	6.6	5.6	
Cocaine	6.5	5.6	5.59**
Ketobemidone	6.5	5.7	
Pipidone	6.2	—	
Methorphinan	5.7	—	
Methadone	5.6	—	

**Value reported by Schoorl, N.* in *Pharm. Weekblad, 76: 1496. 1939.*
***Value reported by Kolthoff* in *Biochem. Z. 162: 289. 1925.*

Phenadoxone was found to be the weakest and methadone the strongest of the narcotic bases. Although both compounds may structurally be regarded as alkanoneamines phenadoxone is a derivative of the weak base morpholine ($pK_B = 5.61$) (14) and methadone a derivative of the strong base dimethylamine ($pK_B = 3.27$) (7). Similar considerations apply to pipidone which compound as a derivative of piperidine ($pK_B = 2.80$) (18) behaves like a strong base.

The hydrophenanthrene-type narcotics, with the exception of methorphinan, were found to be relatively weak bases because of their association with the imino–ethano-linkage. Diamorphine exhibited a lower degree of basicity than morphine, apparently because of the presence of two acetyl groups in the hydrophenanthrene nucleus. Methorphinan on the other hand was found to be much more basic than morphine in spite of the close structural relationship existing between the two compounds. Lack of the ether linkage and particularly lack of the alcoholic hydroxyl group in methorphinan enhances the basicity of this compound (7). These observations clearly show that both nature of the amino-linkage as well as structure of the non-nitrogenous moiety of the molecule determine the strength of narcotics. An investigation of broader scope is presently being carried out at this laboratory in order to obtain further information regarding these relationships. The results of this work are to be published shortly in detail.

It was not possible to correlate pK_B values and product yields. The alkanoneamine-reineckates were all obtained in practically theoretical yields although their pK_B values were found to vary from 5.6–7.8. Conversely, the arylpiperidines whose pK_B values were all found to be approximately 6.5 gave reineckate yields ranging from 80–98%. Of the hydrophenanthrenes codeine gave a relatively low yield of reineckate (82%), yet its pK_B value was found to be practically identical with that of metopon and morphine whose reineckates were obtained in 91 and 95% yields respectively. It must, therefore, be concluded that factors other than the degree of basicity of the organic amine influence the course of the metathetical reaction.

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THE QUANTITATIVE DETERMINATION OF NARCOTICS BY ION EXCHANGE[1]

By Leo Levi[2] and Charles G. Farmilo[3]

ABSTRACT

Codeine phosphate, morphine sulphate, methorphinan hydrobromide, and the hydrochlorides of methadone, phenadoxone, alphaprodine, cocaine, pethidine, diamorphine, dilaudid, morphine, and papaverine were quantitatively determined with a precision of ± 1.6% by ion exchange chromatography. The method was found to be applicable to pharmaceutical preparations and narcotic seizures, provided these did not contain additional ionizing constituents. Use of a solvent system in which the free base remained dissolved throughout the entire process was an important factor in the analysis. The dissociation constants of the narcotics in the solvent systems used are also reported.

INTRODUCTION

The quantitative determination of drugs of addiction constitutes a problem of major importance in clinical as well as in forensic chemistry. The clinical chemist must know the purity of a narcotic before he can accurately study the effect of dosage and the forensic chemist must be able to establish the composition of a narcotic seizure for court purposes. Depending on the size and nature of the sample available for investigation the assay method may involve extraction by solvent partition, formation of suitable derivatives, aquametric or nonaquametric titration, ultraviolet or infrared absorption, polarographic analysis or columnar chromatography.

With the development of synthetic ion exchange resins the usefulness of the chromatographic method as a basic technique for the resolution of complex mixtures and isolation of the individual components was considerably enhanced in practically all its fields of application except narcotic drug analysis. Only one relevant paper describing assays of samples of morphine hydrochloride and tinctures of opium by ion exchange has so far appeared in the literature (2).* The results reported in this publication indicate a high degree of accuracy and precision and since the procedure in turn appeals because of its rapidity and simple technique a detailed study of the method was undertaken in order to evaluate it as a means of recovering and determining narcotics in both C.P. and pharmaceutical preparations.

EXPERIMENTAL

Prior to use the ion exchange resin Amberlite IR-4B was washed successively with distilled water and 95% ethanol in order to remove the "fines" (or color) and traces of extraneous water as well as alcohol soluble chemicals which contaminate it after manufacture. By exhaustive treatment with 4% sodium

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Contribution from the Food and Drug Laboratories, Department of National Health and Welfare, Ottawa.

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**Added in proof: Quite recently a second paper on this subject has been published. (Rasmussen, H.B., Fuchs, D, and Lundberg, L. J. Pharm. and Pharmacol. 4 : 566. 1952.)*

hydroxide it was converted to the hydroxyl form and subsequently washed again with distilled water until the suspension remained neutral for 48 hr. After several washings with ethanol the resin was air-dried until free-flowing and screened to obtain a 40/60-mesh range (U.S. Standard Sieve Series) fraction (average particle size 0.34 mm.) which was slurried into the exchange columns. The all-glass apparatus shown in Fig. 1 was of simple and efficient design. Ground

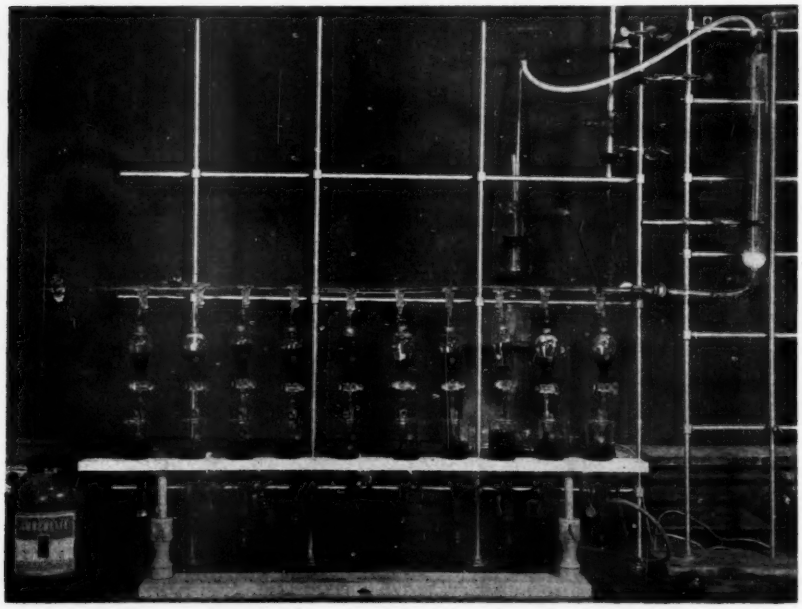

FIG. 1. Ion exchange apparatus.

joints connected the funnels holding the narcotic solution and the tubes containing the resin bed. Flow rates could be conveniently adjusted by stopcock manipulation. The opening of each outlet tube was somewhat above the upper level of the resin bed so that the ion exchanger was covered with liquid at all times and its potential activity kept unaltered. The resin bed was about 10 cm. deep and 1 cm. wide. It was held in place by two small plugs of Pyrex glass wool, one of which rested upon a constriction at the lower end of the column while the other, placed on top, served to keep the packing firm and well in place. After careful backwashing in order to ensure the removal of any air-channels, the system was ready for use.

The accurately weighed quantity of the material to be assayed—usually about 75 mgm.—was dissolved in 2–3 ml. of distilled water, diluted with 50 ml. of a suitable solvent or solvent mixture, and the solution passed at a slow but constant rate (0.05–0.15 ml. per min. per ml. of resin) through the column which had previously been conditioned with about 25 ml. of solvent solution

of the same composition as was employed in the experiment. Another 10 ml. of solvent was used to remove the solution still in contact with the exchanger more efficiently from the resin bed and finally 4 × 5 ml. portions of hot solvent were passed through the column in order to free it from any adsorbate. The effluent solution was collected in a beaker and titrated directly with 0.05 *N* hydrochloric acid using a microburette for measuring the volume consumed and a Beckman pH meter equipped with a glass and saturated calomel electrode for observing the corresponding pH changes. The end point was determined by plotting the volume of the acid consumed vs. the corresponding pH of the solution and graphing V vs. $\Delta V/\Delta$pH in the neighborhood of the equivalence point.

The analysis of pharmaceutical preparations (tablets) was carried out by essentially the same method. Five tablets were ground in a glass mortar and about 50 mgm. of the finely powdered material weighed out accurately. After digestion with 3 ml. of water the triturated mixture was diluted with 50 ml. of the appropriate solvent system. If not all of the material could be dissolved the suspension was filtered to prevent clogging of the resin bed and the assay continued in accordance with the standard procedure.

After each analysis the column was regenerated by passing slowly through it about 25 ml. of a 5% aqueous sodium hydroxide solution, the excess alkali being removed by washing with deionized water until the washings were neutral. The ion exchange resin could thus be activated again and again without losing any of its efficiency.

DISCUSSION

Amberlite IR-4B, the ion exchange resin used in these studies, is a synthetic polyamine and as such a typical anion exchanger. Although the mechanism of its physicochemical reactivity is not yet fully understood it is generally believed (1, 3, 4, 6) that the insoluble, polymeric amine behaves much like a soluble monomeric amine when in contact with water:

$$1. \qquad R{\cdot}NH_2 + H_3O^+ + OH^- \rightleftharpoons [R{\cdot}NH_2{\cdot}(H_3O)^+ \cdot OH^-]$$

where R represents the resin matrix. The passage of an aqueous (or mixed aqueous–nonaqueous) solution of a narcotic salt through the solvated resin bed may be visualized to take place in accordance with the equation:

$$2. \qquad [R{\cdot}NH_2{\cdot}(H_3O)^+ \cdot OH^-] + N_a{\cdot}HX + H_2O \rightleftharpoons [R{\cdot}NH_2{\cdot}(H_3O)^+ \cdot X^-] + N_a + 2H_2O$$

and after elution of the free narcotic base (N_a) has been accomplished conversion of the spent resin to the hydroxyl cycle is brought about by treatment with alkali:

$$3. \qquad [R{\cdot}NH_2{\cdot}(H_3O)^+ \cdot X^-] + NaOH \rightleftharpoons [R{\cdot}NH_2{\cdot}(H_3O)^+ \cdot OH^-] + NaX$$

It was found important that the narcotic base set free in accordance with Equation 2 remained in solution during the entire process because the exchanger on account of its surface, or electrical charge or both, acts also as an adsorbent for charged as well as uncharged coagulated particles formed within the inter-

TABLE I

COMPARISON OF QUANTITATIVE RECOVERIES OF NARCOTICS BY ION EXCHANGE AND REFERENCE METHODS

Narcotic	Solvent system	pK_B of narcotic (20°C.)	Water tolerance (± 1 ml.)	Per cent recovery	
				Ion exchange	Reference method
Alkanoneamines					
Methadone hydrochloride[1]	Methanol–chloroform (2:1)	6.41	25	98.3 96.5 99.4	99.1 (N.N.R. 1951)
Phenadoxone hydrochloride[2]	Methanol–chloroform (2:1)	9.14	25	99.3* 100.4* 97.2*	101.1 (Glaxo Laboratories)
Piperidines					
Alphaprodine hydrochloride[3]	Methanol–ether (1:1)	8.38	∞	100.5 101.1 98.9	99.4 (Hoffmann-LaRoche)
Cocaine hydrochloride	Ethanol–chloroform (2:1)	8.20	18	95.1 95.6 92.8	95.7 (N.F.VIII)
Pethidine hydrochloride[4]	Methanol–ether (1:1)	8.49	∞	99.6 96.4 97.3	98.8 (U.S.P.XIV)
Hydrophenanthrenes					
Codeine phosphate	Ethanol–chloroform (2:1)	6.18	18	96.4 97.1 95.4	96.0 (B.P.1948)
Diamorphine hydrochloride[5]	Methanol–chloroform (2:1)	8.55	25	100.5 101.9 102.2	101.3 (A.O.A.C.1950)
Dihydromorphinone hydrochloride[6]	Ethanol–chloroform (2:1)	8.38	18	97.4 95.7 94.4	96.7 (U.S.P.XIV)
Methorphinan (*dl*) hydrobromide[7]	Methanol–ether (1:1)	7.29	∞	95.8 97.5 98.2	98.6 (Hoffmann-LaRoche)
Morphine hydrochloride	Methanol	7.48	∞	88.9 88.1 91.8	88.5 (B.P.1948)
Morphine sulphate	Methanol	7.48	∞	97.6 94.3 95.3	96.7 (B.P.1948)
Benzylisoquinoline					
Papaverine hydrochloride[8]	Ethanol–chloroform (2:1)	10.09	18	99.1* 98.3* 98.9*	98.5 (U.S.P.XIV)

See facing page for footnotes.

stices of its structure, and large volumes of additional solvent systems were required to elute from the resin bed any material which had precipitated during the ion exchange reaction.

The experimental data are summarized in Table I. The first column lists the narcotics assayed according to their fundamental structural relationships while the second shows the corresponding solvent systems. These contained either methanol or ethanol which component served to enhance the solubility of the free base and at the same time increase the water miscibility of the system. The pK values of the narcotics measured in accordance with the procedure given by Saunders (5) for the particular solvent systems used are reported in the third column. Papaverine and phenadoxone were found to be exceedingly weak bases (basic dissociation constant exponents 10.09 and 9.14 respectively) and the potential break in the titration curves was not sufficiently sharp to locate the equivalence point accurately. These narcotics were therefore determined by gravimetric analysis after careful evaporation of the solvent. The results are shown in Column 5 and values obtained when using other methods of analysis are given in Column 6. No official assay procedures could be found in the literature for methorphinan(*dl*)hydrobromide, the hydrochlorides of alphaprodine and phenadoxone and these narcotics were determined in accordance with the control methods used by their manufacturers. Comparison of the data recorded in the two columns shows that alkanoneamine-, piperidine-, hydrophenanthrene-, and benzylisoquinoline-type narcotics can be quantitatively determined by ion exchange chromatography. The precision of the method as calculated from the experimental data was found to be $\pm$ 1.6% which value compares favorably with that of other narcotic assay methods.

The data given in Table II illustrate that the method is also applicable to pharmaceutical preparations. When carrying out these analyses, all insoluble, inert matter which might be present as a binder, or diluent, should be removed from the solvent system prior to its passage through the resin bed. Also, these preparations must be free from ionizing impurities or non-narcotic constituents which may dissociate and participate in the ion exchange process.

Two heroin seizures obtained from the Narcotic Control Division of the Department of National Health and Welfare, through the Royal Canadian Mounted Police, were also successfully assayed by this method. The results are given in Table III. Both seizures were found by X-ray diffraction to have been heavily adulterated with lactose which did not interfere in the assays.

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* *Determined gravimetrically by evaporation of the solvent.*

1 *Methadone*; (*amidone, Physeptone*^{R}) *dl-6-dimethylamino-4,4-diphenylheptanone-3.*

2 *Phenadoxone*; (*Heptalgin*^{R}) *dl-6-morpholinyl-4,4-diphenylheptanone-3.*

3 *Alphaprodine*; (*Nisentil*^{R}) *dl-α-1,3-dimethyl-4-phenyl-4-propionoxypiperidine.*

4 *Pethidine*; (*Demerol*^{R}, *meperidine*) *ethyl 1-methyl-4-phenylpiperidine-4-carboxylate.*

5 *Diamorphine*; (*Heroin*^{R}, *diacetylmorphine*).

6 *Dihydromorphinone*; (*dimorphone, Dilaudid*^{R}).

7 *Methorphinan (dl) hydrobromide*; (*Dromoran*^{R}) *dl-3-hydroxy-N-methyl morphinan.*

8 *Papaverine*; *3', 4', 6, 7-tetramethoxy-1-benzylisoquinoline.*

Note: The symbol ^{R} *denotes a registered trade-mark. Nonproprietary or official names are used throughout the body of the text.*

TABLE II

QUANTITATIVE DETERMINATION OF NARCOTICS IN PHARMACEUTICAL TABLETS

Tablet	Narcotic content (mgm. per tablet)		
	Labelled amount	Found by	
		Ion exchange	Reference assay
Pethidine hydrochloride	50	48.7 47.2	48.1 (U.S.P. XIV)
Cocaine hydrochloride	70	71.9 70.7	69.3 (N.F. VIII)
	146	142.3 140.9	139.7 (N.F. VIII)
Codeine phosphate	16.2	15.6 14.2	14.9 (B.P. 1948)
Diacetylmorphine hydrochloride	16.2	15.4 15.9	16.1 (A.O.A.C. 1950)
Morphine sulphate	16.2	15.8 16.3	15.7 (B.P. 1948)

TABLE III

ANALYSIS OF HEROIN SEIZURES

	% Heroin	Method
Seizure *A*	45.3	Ion exchange
Seizure *A*	46.8	A.O.A.C. 1950
Seizure *B*	36.4	Ion exchange
Seizure *B*	35.9	A.O.A.C. 1950

The principal condition for success in the analysis is the choice of a solvent or solvent mixture which prevents precipitation of the free base during the ion exchange process, efficiently removes all material held physically at the surface of the exchanger, and stays homogeneous throughout the titration. The solvents shown in Table I were found to fulfill these requirements. Data illustrating the capability of these systems to remain homogeneous on addition of the aqueous phase (titrant) are shown in Column 4 entitled "Water tolerance ($\pm$1 ml.)." Also of marked importance are proper conditioning of the exchanger prior to use, selection of a suitable particle size (0.2–0.4 mm. diameter), correct packing of the column, proper flow rate adjustment, and thorough columnar regeneration.

Regarding its fundamental principle, it is significant to note that the ion exchange method is similar to the classical solvent partition method accepted by the B.P. 1948 and U.S.P. XIV for the analysis of narcotics in that it is based on separation of the free base from its salt. However, the potentialities of ion exchange chromatography in both clinical and forensic chemistry are immeasurably greater because it is a relatively simple and rapid operation and moreover adaptable to the use of small amounts of material.

ACKNOWLEDGMENTS

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They also wish to thank the Resinous Products and Chemical Co. of Philadelphia for the Amberlite IR-4B anion exchange resin used in these studies.

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THE REACTIONS OF CH_3 AND CD_3 RADICALS WITH HYDROGEN AND DEUTERIUM[1]

By T. G. Majury[2] and E. W. R. Steacie

ABSTRACT

The reaction of CH_3 and CD_3 radicals with hydrogen and deuterium have been investigated, acetone being used as a source of methyl radicals. The results indicate (1) that the substitution of D_2 for H_2 has a considerable effect, (2) the substitution of CD_3 for CH_3 has relatively little effect. (3) It is concluded that, contrary to the results of Burton *et al.*, the activation energy of the reaction

$$CH_3 + H_2 \rightarrow CH_4 + H$$

is 9.7 ± 0.6 kcal.

INTRODUCTION

It has been shown (12, 3) that in the photolysis of acetone between 130° and 300° the production of methyl radicals and the formation of methane and ethane are accounted for by the following reactions:

$$CH_3 . CO . CH_3 \rightarrow 2CH_3 + CO \quad (1)$$

$$CH_3 + CH_3 \rightarrow C_2H_6 \quad (2)$$

$$CH_3 + CH_3 . CO . CH_3 \rightarrow CH_4 + CH_2 . CO . CH_3 . \quad (3)$$

Assuming a steady concentration of methyl radicals, it follows that

$$\frac{k_3}{k_2^{\frac{1}{2}}} = \frac{R_{CH_4}}{R_{C_2H_6}^{\frac{1}{2}}\,[Ac]} .$$

In the presence of hydrogen the methyl radicals also react as follows*

$$CH_3 + H_2 \rightarrow CH_4 + H \quad (4)$$

whence

$$\frac{k_4}{k_2^{\frac{1}{2}}} = \frac{(R_{CH_4})_4}{R_{C_2H_6}^{\frac{1}{2}}\,[H_2]}$$

where $(R_{CH_4})_4$ represents the rate of production of methane by reaction (4).

The fate of the H-atom produced in reaction (4) is presumed to be

$$H + CH_3 . CO . CH_3 \rightarrow H_2 + CH_2 . CO . CH_3 .$$

The alternative

$$H + CH_3 \rightarrow CH_4$$

appears to be ruled out as a significant process by evidence obtained in the course of the present work.

MATERIALS

Mallinckrodt Analytical Reagent Acetone was dried successively over sodium

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Contribution from the Division of Chemistry, National Research Council, Ottawa. Issued as N.R.C. No. 2828.

[2]*National Research Council of Canada Postdoctorate Fellow, 1950-51. Present Address: Brooklyn Polytechnic Institute, Brooklyn, N.Y.*

*For a discussion of this reaction, see Reference (14).

sulphate and calcium sulphate and distilled at 56.1–56.5°. The deuterated acetone was prepared by Dr. L. C. Leitch of these Laboratories by the following method.

A mixture of *d*-acetylene and heavy water vapor was passed over a Fe_3O_4–ZnO catalyst at 410° C. The crude product was purified by fractional distillation in a Stedman column at a reflux ratio of 10:1, collecting separately a portion which boiled at 55.5° C. This fraction was further enriched in deuterium by repeated exchanges with heavy water (99.8 mole %) at 60° C. in the presence of a trace of sodium carbonate. Samples taken both before and after enrichment were used in this work, though final quantitative results were based only on work done with the latter. Their compositions were determined by mass spectrometric analysis with the following results:

No. of D-atoms per molecule	Mole % composition I	II
6	86.4	93.2
5	10.2	3.7
4	3.0	3.1
3	0.4	0

The acetone samples were degassed before use to a vacuum of less than 10^{-4} mm. of permanent gas.

The hydrogen used was commercial cylinder gas purified by passage through a palladium thimble. The deuterium, also prepared by Dr. L. C. Leitch, was purified in the same way; mass spectrometric analysis showed the composition to be 95% D_2, 5% HD. The carbon dioxide was commercial cylinder gas which was found to have the composition 99.4% CO_2, 0.6% N_2.

EXPERIMENTAL

The apparatus and method of analysis were similar to those described in earlier papers from this laboratory (17, 16). The radiation from the mercury arc (a Hanovia S-500 lamp) was unfocused but defined by stops so as to fill the reaction cell, which was 4.8 cm. in diameter. In general, no filter was used, so that the absorbed radiation was chiefly at 2537Å; here the extinction coefficient of acetone is 6.7 (13), and, the reaction vessel depth being 10.35 cm. and the pressure of acetone not greater than 10 cm., the absorbed radiation did not exceed 60% of that incident on the cell. Variation of intensity was obtained by interposing a quartz neutral density screen of 27% transmission.

The 2537Å line in the lamp used is strongly reversed so that there was no risk of mercury sensitization. This was confirmed in one instance by a duplicate run using a Corning 9700 filter with a cutoff at 2600Å; no difference in the behavior of the reaction, other than diminished intensity, was detected.

The reactions were carried out to an acetone conversion of less than 10%.

The greater part of the hydrogen remaining after each experiment was removed by passage through a palladium thimble at 350° while the acetone was frozen out in a side-arm. Residual hydrogen was subsequently oxidized over copper oxide along with the carbon monoxide.

In runs involving isotopic mixtures of deuterated methane and ethane with

hydrogen or deuterium it was shown by means of trial experiments that no isotope exchange took place photochemically or thermally in the reaction cell. Exchange at the palladium thimble was found to be negligible, affecting only 1–2% of the reaction products.

The separation of the ethane from the noncondensable gases was effected by means of a Ward–LeRoy still (8).

The mass spectrometric analyses of deuterated methanes and ethanes were made under the direction of Dr. F. P. Lossing of these Laboratories. The analyses for the CD_4–CD_3H mixtures were computed assuming equal sensitivities for the isotopic molecules. The analysis of CH_2D_2 was computed from the spectrum of CH_2D_2 prepared in these Laboratories by Dr. W. A. Bryce. The analysis of CH_3D was computed using C–H and C–D cracking ratios calculated from the spectrum of CH_3D supplied in a private communication by Dr. V. H. Dibeler of the National Bureau of Standards in Washington.

Arrhenius plots of the results were made by the method of least squares; this served also as the basis of calculation of the standard errors of the intercepts and slopes.

Six sets of experiments were performed in all, viz. the photolyses of the normal and deuterated acetones alone, and of each in the presence of hydrogen and deuterium. These will now be described in turn. All quantities of starting materials and products are expressed in molecules per cubic centimeter of reaction volume (190 cc.) and all reaction constants in terms of molecules, cubic centimeters, and seconds. Collision numbers were calculated at 490° K., which is approximately the mean temperature of the photolyses.

1. *The Photolysis of Acetone*

The dependence of this reaction on acetone pressure and light intensity was checked and found to be as predicted by the equation given above for $k_3/k_2^{\frac{1}{2}}$. The results are reported in Table I.

The Arrhenius plot of these results, which is shown in Fig. 1 (open circles), is given by

$$13 + \log \frac{k_3}{k_2^{\frac{1}{2}}} = 5.880 - 2.082 \frac{10^3}{T},$$

the standard errors of intercept and slope being ± 0.062 and ± 0.029, respectively. The slope gives $E_3 - \frac{1}{2}E_2$ as 9.5 ± 0.1 kcal. This agrees well with the values previously reported by Trotman-Dickenson and Steacie (17) (9.7 kcal.) and Nicholson (11) (9.6 kcal.). If the collision diameters of the acetone molecule and the methyl radical are taken as 5.5Å and 3.5Å, the ratio of the steric factors $P_3/P_2^{\frac{1}{2}}$ is found to be $1.9 \pm 0.3 \times 10^{-3}$.

2. *The Photolysis of Acetone in the Presence of Hydrogen*

These experiments were carried out at hydrogen pressures of 5 cm. and 20 cm. The ratio $k_4/k_2^{\frac{1}{2}}$ was found to be independent of hydrogen pressure except at the highest temperature and pressure where a falling-off was noted. The results are presented in Table II and plotted in Fig. 1 (open squares). If the obviously

TABLE I
THE PHOTOLYSIS OF ACETONE

Run	Temp., °K.	Intensity (arbitrary)	[Acetone] molecules per cc. $\times 10^{-18}$	Time (sec.)	Products, molecules/cc./sec. $\times 10^{-13}$			$\frac{k_3}{k_2^{\frac{1}{2}}} \times 10^{13}$
					CO	CH_4	C_2H_6	
A1	413	100	2.27	1800	4.33	0.93	3.42	7.01
A2	405	27	2.33	5400	0.81	0.30	0.53	5.62
B1	409	100	1.07	3600	2.36	0.30	2.05	6.17
C1	409	100	0.58	3600	1.34	0.12	1.19	6.09
D3	498	100	1.90	1200	4.46	3.57	1.50	48.5
D4	499	100	1.87	1200	4.63	3.57	1.49	49.4
D5	494	27	1.94	4800	0.87	0.95	0.13	43.3
F1	494	100	0.46	1200	1.42	0.65	0.79	50.3
G1	565	100	1.68	2400	4.80	5.65	0.52	147
I2	564	100	0.43	2400	1.52	1.29	0.33	168

TABLE II

THE PHOTOLYSIS OF ACETONE IN PRESENCE OF HYDROGEN

Run	Temp., °K.	Acetone concentration molecules/cc. $\times 10^{-18}$	Hydrogen concentration molecules/cc. $\times 10^{-18}$	Time (sec.)	Products, molecules/cc./sec. $\times 10^{-13}$			$\frac{k_4}{k_2^{\frac{1}{2}}} \times 10^{13}$
					CO	CH_4	C_2D_6	
5 cm. hydrogen								
6	412	2.28	1.19	1800	4.10	1.11	3.04	4.12
4	454	2.07	1.03	1800	4.19	2.45	2.11	12.3
8	506	1.90	0.92	1800	4.25	4.41	0.94	35.4
11	523	1.85	0.89	1800	4.24	5.05	0.66	56.0
5	566	1.68	0.86	1800	4.31	6.12	0.33	82.8
10	571	1.70	0.86	1800	4.40	6.38	0.31	85.5
20 cm. hydrogen								
1	409	2.28	4.77	1800	4.24	1.67	2.79	3.68
3	453	2.12	4.41	1860	4.43	3.72	1.58	12.1
7	504	1.90	3.89	1800	4.41	5.90	0.58	35.4
2	567	1.69	3.55	1860	4.88	7.77	0.25	61.1
9	569	1.74	3.38	1800	4.73	7.56	0.26	53.6

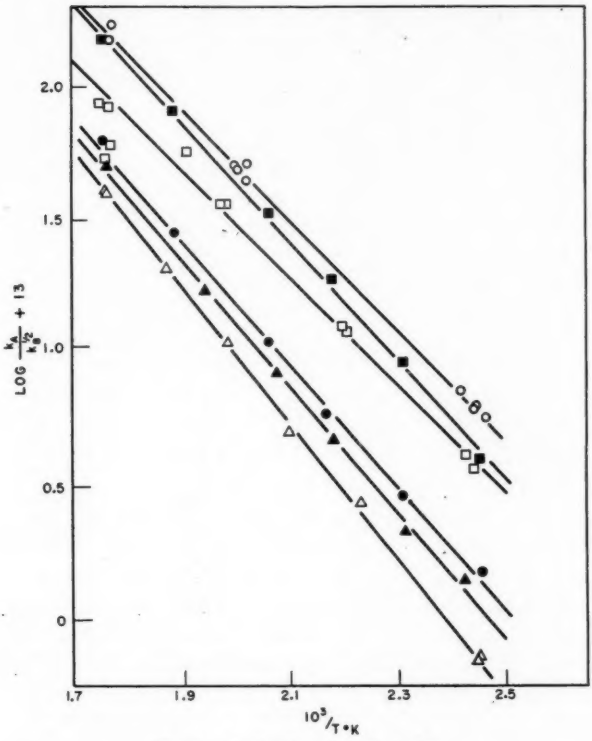

Fig. 1. Arrhenius plot of results.

○ = $CH_3 + CH_3COCH_3$ ● = $CD_3 + CD_3COCD_3$
□ = $CH_3 + H_2$ ■ = $CD_3 + H_2$
△ = $CH_3 + D_2$ ▲ = $CD_3 + D_2$

low results of runs 2 and 9 are omitted, the remainder give the line

$$13 + \log \frac{k_4}{k_2^{\frac{1}{2}}} = 5.508 - 2.009 \frac{10^3}{T}$$

with standard errors of ± 0.125 and ± 0.060 for intercept and slope. The corresponding value for $E_4 - \frac{1}{2}E_2$ is 9.2 ± 0.3 kcal. If 2.8Å is taken as the collision diameter of the H_2 molecule the steric factor ratio $P_4/P_2^{\frac{1}{2}}$ is found to be $7 \pm 2 \times 10^{-4}$.

3. The Photolysis of Acetone in the Presence of Deuterium

In addition to the normal methane formed by reaction (3) we now have deuteromethane formed by

$$CH_3 + D_2 \rightarrow CH_3D + D\,. \qquad (5)$$

The products in this case can be dealt with by two methods. (I) The estimation of $(CH_3D)_5$ by subtracting $(CH_4)_3$ from the total methane; $(CH_4)_3$ is given by the expression $k_3/k_2^{\frac{1}{2}} \times \sqrt{(C_2D_6)} \times [Ac]$. This is the method already used in

Section 2 above. (II) Mass spectrometric analysis of the total methane formed will give the ratio $CH_3D/CH_4 = A$ and hence k_5/k_3 since

$$\frac{k_5}{k_3} = A \times \frac{[Ac]}{[D_2]}.$$

In both cases a small correction is necessary to allow for the presence of 5% HD in the deuterium used since this gives rise to two additional reactions:

$$CH_3 + HD \rightarrow CH_4 + D, \quad (6)$$

$$CH_3 + HD \rightarrow CH_3D + H. \quad (7)$$

Assuming $k_6 = k_4$ and $k_7 = k_5$* it can easily be shown that for Method I the true value of $k_5/k_2^{\frac{1}{2}}$ is given by

$$\frac{R_{(CH_3D)_5} + R_{(CH_4)_6} + R_{(CH_3D)_7}}{R^{\frac{1}{2}}_{C_2H_6} \times \{[D_2] + [HD]\}} - \frac{[HD]}{[D_2] + [HD]} \cdot \frac{k_4}{k_2^{\frac{1}{2}}} = \frac{k_5}{k_2^{\frac{1}{2}}} \text{ uncorrected} - \frac{1}{20} \cdot \frac{k_4}{k_2^{\frac{1}{2}}}.$$

For Method II,

$$\frac{k_5}{k_2^{\frac{1}{2}}} = A \cdot \frac{[Ac]}{[D_2] + [HD]} \cdot \frac{k_3}{k_2^{\frac{1}{2}}} + A \cdot \frac{[HD]}{[D_2] + [HD]} \cdot \frac{k_4}{k_2^{\frac{1}{2}}} = \frac{k_5}{k_2^{\frac{1}{2}}} \text{ uncorrected} + \frac{A}{20} \cdot \frac{k_4}{k_2^{\frac{1}{2}}}.$$

The results obtained using both methods of analysis are presented in Table III and those obtained by Method II are plotted in Fig. 1 (open triangles). They show the expected independence of deuterium pressure. The wide scatter of the results obtained by Method I is due chiefly to the unfavorably low ratio of CH_3D to CH_4, particularly at the low temperatures where the total yield of methane is small, but partly also to the low ethane yield at high temperatures. The coefficients of the Arrhenius plots together with the corresponding ratios of steric factors and energies of activation are as follows:

	Method I	Method II
Intercept	5.60 ± 0.65	6.117 ± 0.064
$P_5/P_2^{\frac{1}{2}} \times 10^3$	$0.2 - 4.6$	3.5 ± 0.5
Slope	-2.35 ± 0.31	-2.559 ± 0.030
$E_5 - \frac{1}{2}E_2$, kcal.	10.7 ± 1.4	11.7 ± 0.1

4. *The Photolysis of d-Acetone*

The mass spectrometric analyses already quoted show that the percentage of fully-deuterated methyl groups was 92.35 in the first and 95.8 in the second sample of *d*-acetone used; the percentage of radicals containing one H-atom was 6.7 in the first and 3.4 in the second sample. Preliminary experiments only were made with the first sample; all final quantitative results are based on experiments made with the more highly deuterated acetone.

By basing our calculations on the fully-deuterated products only, as determined by the mass spectrometer, we can confine our considerations to the following reactions:

$$CD_3 + CD_3 \rightarrow C_2D_6 \quad (8)$$

$$CD_3 + CD_3.CO.CD_3 \rightarrow CD_4 + CD_2.CO.CD_3 \quad (9)$$

$$CD_3 + CD_2H.CO.CD_3 \rightarrow CD_4 + CDH.CO.CD_3 \quad (10)$$

Reaction (10) cannot contribute more than 4% of the CD_4 formed and will

**This assumption is somewhat in error, but since it is only involved in a minor correction it has no appreciable effect.*

TABLE III

THE PHOTOLYSIS OF ACETONE IN PRESENCE OF DEUTERIUM

Run	Temp., °K.	Acetone concentration molecules/cc. × 10^{-18}	Deuterium concentration molecules/cc. × 10^{-18}	Time (sec.)	Products, molecules/cc./sec. × 10^{-12} CO	CH_4+CH_3D	C_2H_6	CH_3D / CH_4	$\frac{k_5}{k_2^{\frac{1}{2}}} \times 10^{13}$ Method I	Method II
5 cm. deuterium										
15	408	2.35	1.28	1800	4.15	0.90	3.22	0.064	1.2	0.72
12	448	2.16	1.11	1800	4.20	1.87	2.38	0.081	0.8	2.73
13	503	1.92	0.95	1800	4.15	3.86	1.11	0.097	8.5	11.0
16	534	1.79	0.92	1800	4.25	4.98	0.63	0.110	26.4	20.7
14	568	1.70	0.89	1800	4.31	5.81	0.36	0.130	25.3	41.5
20 cm. deuterium										
19	409	2.37	4.46	1800	3.96	1.04	3.00	0.202	0.8	0.70
18	476	2.04	3.86	1810	4.19	3.37	1.42	0.280	5.2	5.00
17	568	1.70	3.21	1800	4.21	6.52	0.30	0.447	26.5	40.8

TABLE IV

THE PHOTOLYSIS OF *d*-ACETONE

Run	Temp., °K.	[Acetone] molecules per cc. × 10^{-18}	Time (sec.)	$\%CD_4$	$\%C_2D_6$	Products, molecules/cc./sec. × 10^{-12} CO	CD_4	C_2D_6	$\frac{k_9}{k_8^{\frac{1}{2}}} \times 10^{13}$
54	407	2.30	1800	89.6	95.8	54.1	2.33	46.7	1.48
64	433	2.19	1800	96.4	96.1	56.9	4.33	47.4	2.88
62	461	2.02	1200	92.7	96.0	56.9	7.55	41.9	5.78
60	485	1.92	1230	92.2	94.1	55.3	12.5	36.5	10.8
58	529	1.77	1200	93.5	95.3	54.0	24.5	24.9	27.9
56	569	1.63	1800	93.2	95.5	55.7	39.5	15.5	61.7

contribute less if, as seems likely, the abstraction of an H-atom is more probable than that of a D-atom. Consequently, this reaction has been ignored and the effective concentration of acetone taken as the percentage of CD_3 groups which it contains.

The results of this photolysis are presented in Table IV. The same pressure of acetone (10 cm.) and light intensity were used throughout.

The Arrhenius plot of these results, shown in Fig. 1 (closed circles), is given by

$$13 + \log \frac{k_9}{k_8^{\frac{1}{2}}} = 5.814 - 2.311 \frac{10^3}{T},$$

the standard errors for the coefficients being ± 0.130 and ± 0.059 respectively. The corresponding value for $P_9/P_8^{\frac{1}{2}}$ is $1.8 \pm 0.5.\ 10^{-3}$, and for $E_9 - \frac{1}{2}E_8$, 10.6 ± 0.3 kcal. This agrees with Trotman-Dickenson's value of 10.3 kcal. (17).

The analyses of the ethane produced in these runs showed it to consist of C_2D_6 and C_2D_5H, any $C_2D_4H_2$ present being below the limit of detectability ($\sim\frac{1}{2}\%$). Assigning k_{11} to the combination of CD_3 and CD_2H

$$CD_3 + CD_2H \rightarrow C_2D_5H \qquad (11)$$

and taking the average percentage of C_2D_6 we have

$$\frac{k_{11}}{k_8} = \frac{R_{C_2D_5H}}{R_{C_2D_6}} \times \frac{[CD_3]}{[CD_2H]} = \frac{4.5}{95.5} \times \frac{95.8}{3.4} = 1.3.$$

This value is quite rough, and its difference from unity may not be significant.

A confirmatory calculation on the results obtained from the first sample of acetone gave the average percentage of C_2D_6 as 89.5, whence $k_{11}/k_8 = 1.6$.

5. *The Photolysis of d-Acetone in the Presence of Hydrogen*

This introduces the reaction

$$CD_3 + H_2 \rightarrow CD_3H + H. \qquad (12)$$

The two independent methods of analysis described above are again applicable. For the first method, mass spectrometric analysis was used to estimate C_2D_6/total ethane and $(CD_4 + CD_3H)$/total methane, the latter ratio being required since an appreciable amount of CD_2H_2 was formed by

$$CD_2H + H_2 \rightarrow CD_2H_2 + H. \qquad (13)$$

In both methods, the amount of CD_3H formed from the *d*-acetone itself was estimated from the data given in the preceding section. The results are presented in Table V and plotted in Fig. 1 (closed squares). The intercepts and slopes and the corresponding value of $P_{12}/P_8^{\frac{1}{2}}$ and $E_{12} - \frac{1}{2}E_8$ are as follows:

	Method I	Method II
Intercept	5.895 ± 0.090	6.106 ± 0.085
$P_{12}/P_8^{\frac{1}{2}} \times 10^3$	1.5 ± 0.4	2.5 ± 0.5
Slope	2.148 ± 0.044	-2.230 ± 0.040
$E_{12} - \frac{1}{2}E_8$, kcal.	9.8 ± 0.2	10.2 ± 0.2

The results given by the two methods of analysis are in good agreement.

The amount of CD_2H_2 formed in these experiments, obtained by subtracting the total percentage of CD_4 and CD_3H from 100, is practically constant at 8.2%.

TABLE V

THE PHOTOLYSIS OF *d*-ACETONE IN PRESENCE OF HYDROGEN

Run	Temp., °K.	Acetone concentration molecules per cc. × 10^{-18}	Hydrogen concentration molecules per cc. × 10^{-18}	Time (sec.)	$\%CD_3H$ / $\%CD_4$	$\%C_2D_6$ Total ethane	Products, molecules/cc./sec. × 10^{-12} CO	CD_4	CD_3H	C_2D_6	$\frac{k_{12}}{k_8^{\frac{1}{2}}} \times 10^{13}$ Method I	Method II
55	407	2.33	1.21	1800	56.3/36.2	95.1	53.1	2.09	3.59	43.0	4.39	3.96
65	433	2.16	1.14	1800	56.8/33.8	95.8	—	4.14	6.16	40.9	8.17	9.16
63	459	2.03	1.07	1200	56.7/35.1	95.0	56.8	7.34	11.2	36.3	16.6	18.5
61	484	1.91	0.96	1200	56.3/36.5	95.1	56.5	11.3	14.3	29.1	26.4	32.7
59	530	1.72	0.89	1260	55.6/36.5	92.6	58.7	20.4	27.3	17.5	70.5	80.2
57	570	1.65	0.84	1830	52.6/38.6	88.5	57.7	28.6	36.9	9.0	139	148

TABLE VI

THE PHOTOLYSIS OF *d*-ACETONE IN PRESENCE OF HYDROGEN AND CARBON DIOXIDE

Run	Temp., °K.	Pressure, cm. *d*-Ac	H_2	CO_2	% CD_3H	% CD_4	$\frac{k_{12}}{k_8^{\frac{1}{2}}} \times 10^{13}$, Method II
40	405	9.77	5.06	0	59.8	27.9	3.5
50	413	9.97	4.97	10.5	57.6	28.5	4.6
53	408	10.00	5.31	20.2	57.5	29.8	3.3
49	410	9.97	10.33	20.0	—	—	3.5
45	571	10.13	4.41	0	52.4	36.5	168
52	569	10.02	4.79	10.5	53.0	34.8	157

This is virtually all due to reaction (13), since the amount formed in the photolysis of *d*-acetone alone was undetectably small. We have now

$$\frac{k_{13}}{k_{12}} = \frac{R_{CD_3H_2}}{R_{CD_3H}} \times \frac{[CD_3]}{[CD_2H]} = \frac{8.2}{55.7} \times \frac{95.8}{3.4} = 4.1 .$$

Averaged values for the percentages of methane have been used since the temperature coefficient is evidently too small to determine from these measurements. Using results obtained from the less highly deuterated acetone, the ratio $R_{CD_3H_2}/R_{CD_3H}$, again temperature-independent within the limits of accuracy, was found to be 15.0/71.8 for 20 cm. hydrogen pressure and 12.0/57.5 for 5 cm. hydrogen pressure. This gives k_{13}/k_{12} the value $0.21 \times 92.35/6.7 = 2.9$.

Preliminary experiments with the first sample of acetone yielded evidence on the problem, mentioned in the Introduction, of the fate of the H-atom resulting from the reaction under consideration. It has usually been assumed that this atom would be removed by reaction with an acetone molecule rather than by combination with a methyl radical since the latter reaction seems likely to require a third body. To check this, the photolysis was performed in the presence of carbon dioxide, and the methane composition determined by mass spectrometry. The results, which are given in Table VI, show no increase in the proportion of CD_3H or in the value of $k_{12}/k_8^{\frac{1}{2}}$, indicating that the combination of H-atoms with CD_3 radicals does not occur to any important extent.

6. *The Photolysis of d-Acetone in the Presence of Deuterium*

Since the deuterium used contained 5% HD, fully deuterated methane could be formed by the following two reactions:

$$CD_3 + D_2 \rightarrow CD_4 + D \qquad (14)$$

$$CD_3 + HD \rightarrow CD_4 + H \qquad (15)$$

as well as by reaction (9) above. Evidently the error will not be great if we assume $k_{15} = k_{14}$, giving

$$\frac{k_{14}}{k_8^{\frac{1}{2}}} = \frac{(R_{CD_4})\ \text{total} - (R_{CD_4})_9}{R_{C_2D_6}^{\frac{1}{2}} \times \{[D_2] + [HD]\}} .$$

Mass spectrometric analysis was used to determine the percentages of fully deuterated material in the products. The results are presented in Table VII.

The Arrhenius plot of these results, which is shown in Fig. 1 (closed triangles), is given by

$$13 + \log \frac{k_{14}}{k_8^{\frac{1}{2}}} = 5.869 - 2.376 \frac{10^3}{T} ,$$

the standard errors for intercept and slope being ± 0.130 and ± 0.061 respectively. The corresponding value of $P_{14}/P_8^{\frac{1}{2}}$ is $2.0 \pm 0.6 \cdot 10^{-3}$, and of $E_{14} - \frac{1}{2}E_8$, 10.9 ± 0.3 kcal.

The methane formed in these experiments was composed of CD_4 and CD_3H, the amount of CD_2H_2 being undetectably small. Assigning k_{16} to the reaction

$$CD_2H + D_2 \rightarrow CD_3H + D \qquad (16)$$

and using the average value of the methane composition we have

TABLE VII

THE PHOTOLYSIS OF *d*-ACETONE IN PRESENCE OF DEUTERIUM

Run	Temp., °K.	Acetone concentration molecules/cc. × 10^{-18}	Deuterium concentration molecules/cc. × 10^{-18}	Time (sec.)	% CD_4	% C_2D_6	Products, molecules/cc./sec. × 10^{12} CO	CD_4	C_2D_6	$\frac{k_{14}}{k_5^{\frac{1}{2}}} \times 10^{13}$
66	412	2.30	2.30	1800	88.8	95.7	55.4	4.75	47.3	1.40
67	432	2.11	2.23	1800	92.0	95.6	—	7.10	42.4	2.13
68	458	1.98	2.16	1800	92.0	95.5	54.3	13.6	39.2	4.69
71	481	1.95	2.05	1200	92.6	95.0	58.3	21.7	34.1	8.40
70	514	1.79	1.93	1200	92.4	94.4	60.1	35.6	25.7	17.1
69	567	1.64	1.75	1200	92.2	92.4	59.2	61.2	11.9	50.2

TABLE VIII

THE REACTIONS OF CH_3 AND CD_3 RADICALS WITH HYDROGEN, DEUTERIUM, AND THE PARENT ACETONE

Reaction	$\frac{k_A}{k_B^{\frac{1}{2}}} \times 10^{13}$, cc.$^{\frac{1}{2}}$ molecules$^{-\frac{1}{2}}$ sec.$^{-\frac{1}{2}}$ 130°C.	210°C.	290°C.	$\frac{P_A}{P_B^{\frac{1}{2}}} \times 10^3$	$E_A - \frac{1}{2}E_B$, kcal.
$CH_3 + CH_3.CO.CH_3$	5.2	37	151	1.9 ± 0.3	9.5 ± 0.1
$CH_3 + H_2$	3.3	22	87	0.7 ± 0.2	9.2 ± 0.3
$CH_3 + D_2$	0.6	6.6	37	3.5 ± 0.5	11.7 ± 0.1
$CD_3 + CD_3.CO.CD_3$	1.2	10.7	51	1.8 ± 0.5	10.6 ± 0.3
$CD_3 + H_2$	3.7	31	140	2.5 ± 0.5	10.2 ± 0.2
$CD_3 + D_2$	0.9	8.9	46	2.0 ± 0.6	10.9 ± 0.3

$$\frac{k_{16}}{k_{14}} = \frac{R_{CD_3H}}{R_{CD_4}} \times \frac{[CD_3]}{[CD_2H]} = \frac{8.0}{92.0} \times \frac{95.8}{3.4} = 2.5.$$

The values of the ratios k_{16}/k_{14} and k_{13}/k_{12} indicate that CD_2H radicals react somewhat faster than CD_3 radicals with H_2 and with D_2. This is surprising, since the ratios for CH_3/CD_3 have been accurately measured and are definitely slightly less than unity. This suggests that CD_2H radicals react somewhat faster than either CH_3 or CD_3. The ratios for CD_2H/CD_3 are, of course, very rough since they involve the values of R_{CD_3H} and of $[CD_2H]$, both of which are small and cannot be determined with high accuracy. It does, however, appear that the ratios are significantly greater than unity.

DISCUSSION

The results are summarized in Table VIII. k_A, E_A, and P_A refer to the reaction between the methyl radical and the molecule in question and k_B, E_B, and P_B to the combination of the two methyl radicals.

Recent work on the combination of CH_3 radicals (6, 4, 9, 10, 5) indicates that median values for P_B and E_B can be accepted as $\simeq 0.3$ and zero respectively, and these values are no doubt valid also for the combination of CD_3 radicals. The figures in the last column of Table VIII can therefore each be taken as the actual energy of activation of the reaction in question, and the absolute steric factors can be obtained from the figures in the preceding column by dividing throughout by $\simeq 2$.

The values of P_A and E_A for the reactions of CH_3 radicals with hydrogen and deuterium differ appreciably from those recently published by Anderson, Davison, and Burton (1). However, Wijnen (19) has shown that a recalculation of their data gives results in reasonable agreement with the present values.

Isotope Effects

The standard errors quoted for the activation energies indicate their experimental precision, but, having regard to small uncertainties of mechanism, their true physical significance is probably better expressed by a general variance of ± 0.3 kcal. or more. It is clear that this variance, being fairly large relative to the experimental differences, precludes any very precise interpretation of the results. However, it seems possible to draw two general conclusions regarding isotope effects. First, comparing the reactions of the CH_3 radical with those of the CD_3 radical, there is no consistent evidence of any significant difference in their behavior. Second, comparing the reactions of hydrogen with those of deuterium, it will be seen that the latter require the higher activation energies, the average value of the difference being 1.6 ± 0.6 kcal. This is roughly in agreement with theory (2) which predicts that at low temperatures the difference in activation energies for reactions of isotopic molecules should approach the difference in their zero-point energies, which in this case is 1.8 kcal.

The values of both P and E for the reaction of CH_3 with D_2 are somewhat out of line with the others. It is probable that in this case errors in E and P compensate one another, and that the real values of both may be somewhat

lower. All that can be said for the moment is that for both CH_3 and CD_3 the results can be expressed by the average values

$$\begin{aligned} &CH_3(\text{or } CD_3) + H_2 \qquad E = 9.7 \pm 0.6 \text{ kcal.} \\ &CH_3(\text{or } CD_3) + D_2 \qquad E = 11.3 \pm 0.6 \text{ kcal.} \end{aligned}$$

It is also instructive to consider the relative values of the rate constants at a given temperature, since here the results are not affected by compensating errors in E and P, and such relative values should therefore be somewhat more precise. Thus at 210° C., for the ratios of values of $k_A/k_B^{\frac{1}{2}}$ we have

$$\left.\begin{aligned} \frac{CH_3 + H_2}{CH_3 + D_2} &= 3.3 \\ \frac{CD_3 + H_2}{CD_3 + D_2} &= 3.5 \end{aligned}\right\} \text{Average} = 3.4, \qquad \left.\begin{aligned} \frac{CH_3 + H_2}{CD_3 + H_2} &= 0.71 \\ \frac{CH_3 + D_2}{CD_3 + D_2} &= 0.74 \end{aligned}\right\} \text{Average} = 0.7.$$

This gives further confirmation of the considerable effect of the substitution of D_2 for H_2 and the relatively small effect of the substitution of CD_3 for CH_3.

In one case information is available on the corresponding reaction of ethyl radicals, since Wijnen and Steacie (18) have investigated the reaction

$$C_2H_5 + D_2 \rightarrow C_2H_5D + D. \tag{17}$$

Comparing this with

$$CH_3 + D_2 \rightarrow CH_3D + D \tag{5}$$

we have

	E, kcal.	$P/P_B^{\frac{1}{2}}$
$C_2H_5 + D_2$	13.3 ± 0.5	10^{-3}
$CH_3 + D_2$	11.7 ± 0.3	3.5×10^{-3}.

There thus appears to be little difference in the steric factors of the two reactions. The fact that E_{16} is somewhat higher than E_5 is in line with the lower value of the bond dissociation energy of C_2H_6, which makes reaction (17) 3 or 4 kcal. more endothermic than (5).

In view of the fact that the value of the bond dissociation energy $D(CH_3\text{–}H)$ is well established at 101 ± 1 kcal. (7) and that D(H–H) is accurately known, we may write

$$E = 9.7 \pm 0.6 \text{ kcal.}$$
$$CH_3 + H_2 \underset{E_R}{\overset{\longrightarrow}{\underset{\longleftarrow}{\qquad}}} CH_4 + H \quad -2.2 \pm 1 \text{ kcal.}$$

Hence, for the activation energy of the reverse reaction

$$E_R = 9.7 - 2.2 = 7.5 \pm 1.6 \text{ kcal.}$$

Considerable work* has been done on this reaction. The experimental results are consistent with a value of about 13 ± 2 kcal. for the reaction if a steric factor of 0.1 is assumed. It has been suggested that the results which lead to a value of the temperature coefficient should not be taken too seriously (15) and that perhaps the best value should be taken as $E = 10.9$ kcal., $P = 10^{-2}$. In

*See Reference (14) for a discussion of the experimental results.

view of the fact that methane does not react with H-atoms under conditions where other hydrocarbons do so, it is very difficult to reconcile the results with a lower value of E than this unless P is also low. If we take 9 kcal. as the extreme upper limit of E_R calculated from the present work, we are still left with a discrepancy of about 2 kcal. which must be taken care of by the steric factor. It may, therefore, be concluded that the present results can only be reconciled with the results on the reaction of H-atoms with methane if the latter reaction has a steric factor of the order of 10^{-4}.

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NOTES

On the Liquid–Vapor Coexistence Curve of Xenon in the Region of the Critical Temperature. II*

In a recent paper (1) by two of the authors (M.A.W. and W.G.S.) it was shown that the density range of the flat top of the coexistence curve of xenon depended on the vertical length of the observation bomb and could be qualitatively explained on the basis of the van der Waals isotherm when hydrostatic effects were taken into account. It was realized that the actual critical xenon isotherm would be much flatter near the critical density than the van der Waals isotherm and would probably give more closely agreeing values for the observed width of the flat top of the coexistence curve.

One of us (H.W.H.) has now determined the isotherm of xenon at the critical temperature 16.590° C. in a horizontal bomb of vertical height 1.6 cm.** The isotherm is indeed considerably broader than the van der Waals isotherm. The calculation of the flat top width of the coexistence curve as a function of vertical bomb length was carried out as described previously (1). The results are shown in Fig. 1. Curve *A* was calculated from the actual isotherm and curve *B*, calculated from the van der Waals isotherm, is the same as that given previously (1).

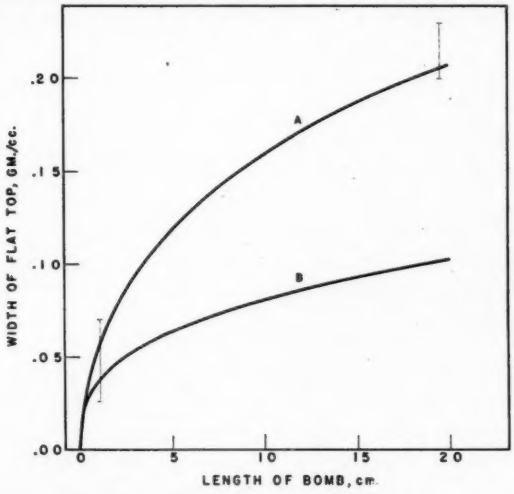

Fig. 1. Density range of flat top of coexistence curve of xenon as function of bomb length.
Curve *A*: Calculated from Habgood's Isotherm at 16.590°C.
Curve *B*: Calculated from van der Waals Isotherm.
Length of vertical lines is a measure of the uncertainty of the observed flat top widths for the two bombs used.

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** *The data are being prepared for publication.*

The vertical lines show the observed flat top widths for the two bombs used. The length of the lines is a measure of the uncertainty of the flat top density range which is due to the fact that the ends of the flat portion of the coexistence curves could not be determined precisely.

Actually the short bomb used was an ordinary long bomb turned on its side so that its vertical cross section was circular rather than rectangular. The calculation was, however, repeated for a circular vertical cross section and the result for a bomb length 1.2 cm. was only 2.5% higher than that given by curve *A*.

As the isotherm was determined in a bomb of finite vertical height it will be somewhat broader than the true isotherm corresponding to an infinitesimally short bomb. Curve *A* calculated from this broader curve therefore represents an upper limit for the variation of flat top width with bomb length.

These calculations thus appear to support our previous conclusion that gravitational effects are capable of explaining the whole of the flat top width of the observed coexistence curves.

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An Important Reflectance Correction in Light-scattering Studies*

In the course of investigations of the properties of polymers of high molecular weight by the light-scattering method, anomalous results were obtained, which were found to be due to reflection of light at a glass–air interface. The reflection that was found to be important was that of the primary beam back into the scattering volume. In this work the Light-scattering Apparatus "B" described by Hadow, Sheffer, and Hyde (2) was used. A substantially parallel beam of light passes through a solution of the polymer contained in a glass cell of such a construction that the beam on leaving the cell is normal to the wall of the vessel and the scattered light can be observed at angles of 33°, 60°, 90°, 120°, and 147° to the path of the beam. The *direction* of the light beam is important since the interference between the light waves scattered from different portions of the large molecules in the solution results in an asymmetric scattering envelope. If a fraction of the light beam is reflected *backwards* when the light leaves the cell, a second envelope which is asymmetric in the opposite direction will be superimposed on the original pattern of scattered light. The total scattered light at each angle now measured will give an erroneous picture of the extent of the interference of the light waves and therefore of the size of the scattering particle.

The fraction of the incident light that is reflected back from the glass–air interface (where the light leaves the cell) can be calculated from the formula

$$R = \frac{(n_2 - n_1)^2}{(n_2 + n_1)^2}$$

where R is the fraction of the incident light that is reflected from an interface formed by a medium of refractive index n_2 immersed in a medium of refractive index n_1. Using $n_2 = 1.55$ for glass, and $n_1 = 1.00$ for air, a value of $R = 4.7\%$ of the intensity of the incident beam is obtained. When the cell contains a liquid of refractive index considerably different from that of the glass there will be an additional reflection from the liquid–glass interface. In the case of water ($n = 1.33$) this reflection amounts to 0.6% of the incident beam. When benzene solutions are used in the cell the liquid–glass reflectance correction is negligible.

Benzene solutions of a polystyrene fraction of molecular weight of approximately 4×10^6 were used in this investigation. Fig. 1 shows the light-scattering data plotted according to the method of Zimm (4). The concentration c is in gm. per ml., I is the reduced intensity of scattering based on benzene as a standard, and θ denotes the angles at which the scattered light is measured. It is obvious that the values obtained at 120° and 147° are quite anomalous and that only the data for the forward angles can be used in the extrapolation to $\theta = 0$ and $c = 0$.

Fig. 2 shows the same data after applying corrections for the scattering due

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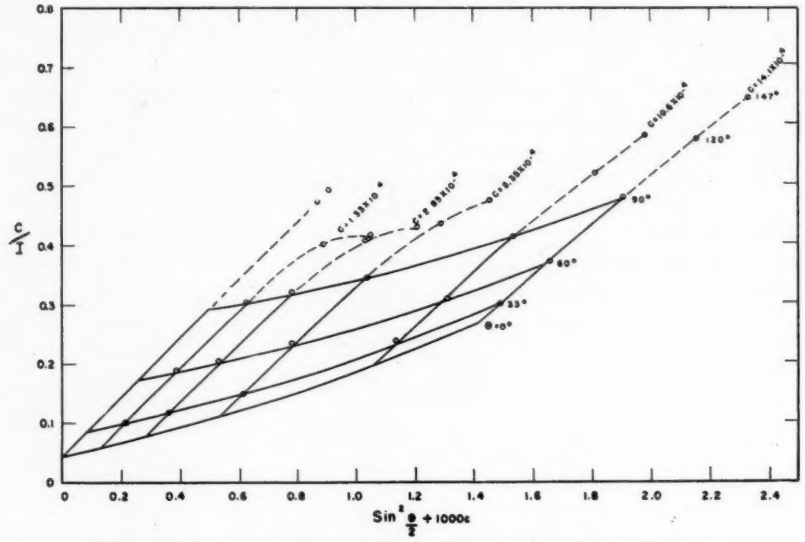

Fig. 1. Zimm plot of light-scattering data uncorrected for reflection.

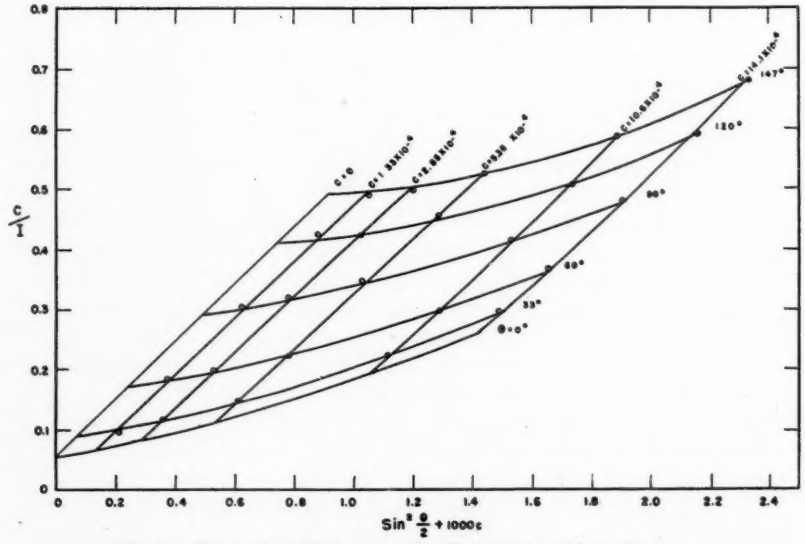

Fig. 2. Zimm plot of light-scattering data corrected for reflection.

to the 4.7% of the incident light reflected at the interface at the exit side of the cell. The corrections were made by reducing the measured scattering at 90° by 4.7%, deducting from the measurements at the backward angles 4.7% of the values at the corresponding forward angles and from those at the forward angles 4.7% of the reduced scattering at the corresponding backward angles. Only a second-order error is introduced in using apparent rather than true forward scattering in the reduction of the scattering at the backward angles. Where the dissymmetry of the scattering is large, the corrections for the backward scattering can be of considerable magnitude. In this case the largest correction ($\theta = 147°$, $c = 1.33 \times 10^{-4}$) amounts to a reduction of 20% of the apparent scattering. In comparing Figs. 1 and 2 the greater self-consistency of the corrected data is very obvious.

The Zimm method of plotting light-scattering data is applicable only in those cases in which the equipment used permits measurement of the scattered light at a sufficient number of angles to allow satisfactory extrapolation of the data. In the majority of cases reported in the literature measurements have been made at 90° and at two equal angles about 90° (most frequently 45° and 135°). From these measurements it is necessary to obtain the limiting dissymmetry at zero concentration, the dissymmetry being defined as the ratio of the intensity of light scattered at the forward angle to that at the corresponding backward angle. Dissymmetry data for the polystyrene fraction are given in Fig. 3 in which the dissymmetry coefficient, $q = \frac{I_{33°}}{I_{147°}} - 1$. The top curve shows

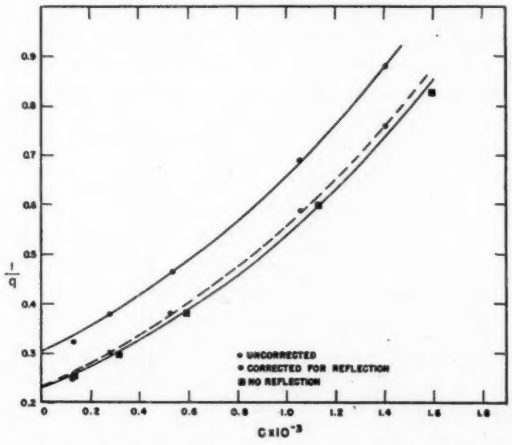

Fig. 3. Reciprocal of the dissymmetry coefficient plotted against concentration.

the uncorrected data, while the dotted curve gives the data corrected for reflection in the manner described above. The limiting dissymmetries differ by 20%. Using the theoretical variation of scattering intensity with angle for random coils (3) it is possible to calculate a correction factor from the dis-

symmetry in order to correct the 90° scattering and obtain the true turbidity. In this case the correction factors differ by 27% and thus the molecular weight of the polystyrene fraction calculated from the data uncorrected for reflection is 27% lower than the true value. (The percentage error in $\left(\frac{I_{60°}}{I_{120°}}\right)_{c=0}$ amounts to only 8% but the shapes of the correction factor curves are such that the error in the correction factor is approximately the same as above.)

The dissymmetry data can also be used to calculate the root-mean-square length of the chain (1, 3). In this case the value obtained is approximately 15% too low using the uncorrected data.

Instead of correcting arithmetically for the reflection it is possible to eliminate it by proper design of the light-scattering cell. This is taken care of in the cell of Zimm (4) for example, by using a vessel with sloping walls so that the reflected light does not follow the path of the incident beam. However, most existing light-scattering apparatus, including the two types available commercially, make use of cells with parallel walls perpendicular to the path of the light. In these cases it has been shown that the reflectance correction is very important particularly when dealing with solutes of very high molecular weight.

It was found that the reflection at the glass–air interface could be substantially eliminated by means of easily applied additions to standard light-scattering cells. The most satisfactory arrangement investigated was to cement a tube to the outside of the cell so that the light beam on leaving the cell traveled down the axis of the tube. The inside of the tube was blackened to prevent reflections. The open end was cut at an angle of about 60° and a piece of glass cemented over it. The tube was then filled, through a small hole in the top, with a liquid having a refractive index close to that of the glass. The reflections were then negligible at all interfaces except the final glass–air one and this reflection could not reach the light-scattering cell. When polarized light was used a piece of polaroid cemented to the cell was also reasonably effective in eliminating the reflection.

With the apparatus modified to eliminate the interfacial reflection on the exit side, the measurements were repeated. Using the Zimm plot the results were substantially the same as those given in Fig. 2. The measured dissymmetries are shown in the bottom curve of Fig. 3 and can be seen to differ only slightly from the values obtained by applying the reflectance correction to the original data. This is further proof of the validity and importance of the reflectance correction.

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